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WHO SHOULD TREAT PELVIC CANCER?*

Presidential Address

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PUBLIC concern over the dangers of nuclear fall-out demands that obstetricians and gynecologists improve their knowledge of radiation hazards and act to protect women and their babies against uncontrolled exposure to ionizing radiation. The numerous uses of irradiation for the female should be carefully reviewed with regard to the genetic and somatic effects. The place of the gynecologist in the treatment of malignant disease of the female pelvic organs should similarly be defined.

In the infancy of therapeutic radiation the gynecologist, working with such physicists as Failla, Quimby, and Glasser, employed radium not only for malignant disease of the female genitals but also for many benign conditions such as dysfunctional bleeding, bleeding due to myomas, endometriosis, and intractable dysmenorrhea. A number of gynecologists of those days—Kelly, Schmitz, Clark, and Healy, to mention a few—contributed greatly to the knowledge of radiotherapy of cancer in the female.

In 1956 a committee of radiation therapists met with representatives of the Medical and Scientific Committee of the American Cancer Society to seek

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financial aid for advanced training in radiation therapy. It was their contention that in the regular three-year training program in radiology it was impossible to develop a therapist versed in supervoltage irradiation as well as conventional therapy. As a result of this meeting there now exist fellowships for advanced training in radiation therapy, which are granted by the American Cancer Society for three years, carrying stipends of six, eight, and ten thousand dollars per year. Similar fellowships are available to trainees in gynecologic cancer.

Howard Taylor, in his presidential address before the American Gynecological Society, stressed the need for cooperation rather than competition between gynecologists and those interested in similar problems. He envisioned a department of gynecology and obstetrics with men especially trained in oncology so that the therapy offered to these patients would be optimal. That such a plan is necessary was demonstrated by a study of "haphazard therapy" which we made some years ago.

Arneson has stated, "Irradiation therapy has cured more cervical cancer than any other method." He cautions, however, that radium is available to any physician and that not all radiologists are trained in therapy. Therefore, to refer patients to the Department of Radiology, as is being done in many communities, may be disastrous. Arneson suggests that the radiation therapist should be chosen with the same care and consideration employed in the selection of any other consultant.

Here, then, is evident need for cooperative effort. To the gynecologist falls the responsibility of early diagnosis, aimed at finding cancer in the preinvasive or preclinical stage. Cooperation with the cytologist, pathologist, and therapeutic radiologist is necessary to determine the extent of spread, the type of therapy, the degree of sensitivity, and the amount of dosage. If the radium and x-ray are to run concurrently, then the radiologist begins with the external therapy, having planned the number of fields and the daily dose in relation to the depth, area, and absorption previously determined by measurements of the patient. Again, the type of radium applicator and its loading depend on the configuration of the patient and the tumor.

The application, however, must be done by one who is experienced in pelvic anatomy and its anomalies, and who has developed a sense of touch to identify tissue resistance, thickening, and fixation. The management of the bladder and rectum to prevent injury is most important, as are direct recordings of the amount of irradiation reaching the rectal and bladder mucosa.

Let us reiterate that the use of radium in pelvic cancer originated through the efforts of gynecologists. X-ray therapy was introduced by diagnostic radiologists who, without knowing the depth or tumor dose, developed a trial and error method which was measured in time of radiation administered at a certain distance. To the physicist belongs the credit for developing the refined techniques in use today.

Radium insertion, whether by tandem, implantation, or needling, is a surgical procedure accomplished in the surgical unit and accompanied by the surgical hazards of rupture of the uterus, stenosed endocervix, malposition,

hematometra, pyometra, sepsis, injury to a neighboring viscus, and hemorrhage. Therefore this procedure must remain in the hands of those trained in surgery, as surely as the operation of the present-day supervoltage apparatus belongs to radiation therapists.

To accomplish this cooperative teamwork let us encourage the preparation of our trainees in the treatment of cancer. In Chicago, our fourth-year resident applies for an American Cancer Society or National Health Institute traineeship which will pay him three thousands dollars per year. The granting of this traineeship depends on the agencies approval of the faculty, material, and program offered by the institution sponsoring the application. The trainee's work during this year is limited to the field of cancer. Through the graciousness of one of our outstanding radiation physicists, a course is offered in radiation physics to all Chicago trainees on cancer programs. This arrangement obviates the difficulty of each program's supplying this necessary information to its participants. An advantage could be gained if such a course were given for gynecologic trainees separately, for the course need not include such highly technical matters as the construction of an x-ray apparatus. Such a course could be held at a convenient center and the cost absorbed by all participating institutions.

This knowledge is placed into practice when the trainee working with our therapeutic radiologist and his staff measures the patients, plots the measurements, and figures the dose. He spends sufficient time in the radiation department to do this for each patient with gynecological cancer. On the days radium work is done the candidate brings the radium applicator, which he saw loaded for the particular case on hand, to the surgical department, and supervises sterilization of the applicators, needles, or seeds. Before insertion of the radium the case is reviewed in the presence of the radiology trainees. Conditions of the urinary tract and lower bowel are discussed. Examination under anesthesia is repeated to recheck the staging. Then the placement and packing are accomplished.

Measurements with the oscillator are made and if the dose measured in the bladder or rectum is too high, replacement and repacking are done. When seeds or needles are employed, lateral, anterior, and posterior films of the pelvis are taken so that the dose can be accurately determined by indirect calculation. Radium is removed by the trainee in gynecology who notes the time, number of packs, etc., on the record. He then cleanses the capsule or applicators and returns the radium to the radiologist or his responsible designee, who re-stores it in the proper receptor. Smear studies are continued. Bowel and urinary tract complications are combated and skin reactions allayed by proper care. Both the radiologist and the gynecologic trainee visit the patient in her room daily, the trainee being responsible for recording his observations and her progress.

Follow-up is most important and is carried out by digital examination, smears, and visualization of the cervix. Cystoscopy, proctoscopy, radiography, biopsy, and curettage are employed when indicated. Those of us who have

accomplished this routine many times realize that digital examination is the most important single procedure. How frequently a patient with intractable pain comes to our attention with uninjured bladder, urinary tract, or lower bowel, a healed cervix, and yet an undetected spread of the disease to the obturator or iliac nodes, overlooked by those not familiar with digital detection!

Too many patients are still being denied surgical help when radiation has failed. Our studies have shown that detection of persistent or residual disease when accomplished early results in a high salvage through surgical intervention. Such early detection is again facilitated by the digital and visual familiarity with the pelvis. That exenteration has a place in carefully selected advanced cervix cancer is borne out by our ten years' experience with the procedure. The trainee participates in the selection of cases for surgical interference, and assists or performs under supervision the indicated surgical procedure.

Many history-making events in our specialty have had their development in the Mississippi Valley. Let us now assemble the strength of this organization to solicit help from the College and sister societies to organize a cancer training program which will result in a cooperative program of therapy. Let the Central be known for its contribution to the treatment of pelvic malignancy as it is known for its maternal welfare studies.

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LYMPHOCYSTS: A COMPLICATION OF RADICAL PELVIC SURGERY*

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A FREQUENT, serious postoperative complication of pelvic lymphadenectomy is an accumulation of fluid in the retroperitoneum at the dissection site. Following removal of the lymph nodes and adipose tissue, an actual or potential space is created which is bounded laterally and posteriorly by the denuded muscular walls of the pelvis and medially by the stripped peritoneum. In the majority of the cases obliteration of the artificial compartment occurs promptly. In approximately one fourth of the patients, however, a pool of lymphlike fluid maintains or augments the volume of the dissection space (Fig. 1). The resulting mass produces varying pressure effects on the ureters, bladder, rectosigmoid, and blood vessels. These effects may be minimal or sufficiently severe to interfere with the function of these structures, thereby significantly prolonging postoperative morbidity.

Review of the Literature

The only report in the American literature which deals specifically with this subject is that of Gray, Plentl, and Taylor,[1] published in May, 1958. This is surprising since during the last 10 to 15 years the revival of interest in the surgical treatment of patients with carcinoma of the cervix has resulted in a large number of lymphadenectomies being performed.

Gray and associates made the diagnosis of lymphocysts 9 times in 55 pelvic lymphadenectomies (16.4 per cent) and they feel that others may have escaped detection. These authors consider this complication responsible for a large portion of the morbidity and mortality resulting from the operation. In their opinion, without an effective method of prevention of the formation of lymphocysts, the routine performance of pelvic lymphadenectomy following radiotherapy should be abandoned.

The Japanese literature contains several reports describing lymphocyst formation following combined radical hysterectomy and pelvic lymphadenectomy. Mori[2] made a very comprehensive study of 68 lymphocysts following 140 Okabayashi operations for carcinoma of the cervix. His incidence of 49 per cent is generally higher than quoted, although one author has indicated an incidence of 58.1 per cent. Mori concludes that the frequency of this complication is dependent upon the extent of operative interference with the

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pelvic lymphatic system. In his experience, the greater the size of the specimen and the number of nodes excised, the higher the incidence of lymphocysts. Advanced stages of carcinoma, excess blood loss at the time of the operation, or the development of postoperative infection did not seem to contribute appreciably to the formation of lymphocysts in his series.

Material

Pelvic lymphadenectomy has been performed as an investigative and therapeutic procedure on 281 patients at The University of Texas M. D. Anderson Hospital and Tumor Institute from January, 1955, to July, 1958. Of these 281 patients, 266 were first treated with irradiation. Our customary doses of radium and x-ray were not reduced to favor the operation which

A. *B.*

Fig. 1.—*A* and *B*, Opacification of bilateral lymphocysts following aspiration. These are the commonest locations for these collections. Although their size is seemingly not excessive, the patient had extensive edema of the right lower extremity and genitals and a right hydronephrosis and hydroureter. The left leg and ureter were normal because of the relatively high position of the left cyst. The metallic clips are hemostatic agents used at the time of operation.

followed from 6 to 12 weeks later. In all patients the operative technique and the extent of the dissection were essentially the same. However, a hysterectomy was performed at the same time in 81 patients.

TABLE I. LYMPHOCYST FORMATION ACCORDING TO DISEASE

DISEASE	CASES	LYMPHOCYSTS	%
Squamous Carcinoma of the Cervix.—			
Stage I	11	2	18
Stage II	44	14	32
Stage III	129	39	30
Complicated by pregnancy	7	2	29
Cervical stump	2	0	
Recurrent	6	2	33
Unstaged	16	2	12
Limited Invasion	3	1	33
Adenocarcinoma.—			
Corpus uteri	51	4	8
Corpus et colli	12	2	17
Total	281	68	

The primary disease in most of the patients was International Classification Stage III squamous cell carcinoma of the cervix. Squamous cell carcinomas of the cervix complicated by other clinical factors and adenocarcinomas of the corpus were also reviewed. The number of patients in each group and the incidence of lymphocyst formation are shown in Table I.

TABLE II. SIZE OF LYMPHOCYSTS ACCORDING TO THE ADVANCEMENT OF SQUAMOUS CARCINOMA OF THE CERVIX

SQUAMOUS CARCINOMA CERVIX	LYMPHOCYSTS	SMALL	MEDIUM	LARGE
Stage I (11)	2	2 (100%)		
Stage II (44)	14	9 (64%)	1 (7%)	4 (29%)
Stage III (129)	39	22 (56%)	9 (23%)	8 (21%)

TABLE III. LYMPHOCYST FORMATION IN PATIENTS WITH CARCINOMA POSITIVE AND NEGATIVE NODES

TYPE OF NODES	NUMBER OF LYMPHADENECTOMIES	LYMPHOCYSTS
Negative	235	51 (22%)
Positive	46	17 (37%)
Total	281	68

The uncomplicated squamous cell carcinomas of the cervix in Table II show no increased incidence of lymphocyst formation from Stages II and III. Nor does Table II show any significant increase in the size of the lymphocysts. Where positive nodes were found (Table III), however, the incidence definitely increased.

Symptomatology

The clinical importance of a lymphocyst is determined by its size and location. In general the smaller collections are well tolerated and tend to regress spontaneously; the larger cysts produce greater immediate discomfort and more frequent and more severe sequelae. However, this is not necessarily the case, as is demonstrated in Fig. 2. This large lymphocyst displaces the ureter but does not impair function. Its high position in the pelvis provides space for expansion without compression of the adjacent viscera.

TABLE IV. POSTOPERATIVE PERIOD WHEN DIAGNOSIS OF LYMPHOCYST WAS ESTABLISHED

TIME	NUMBER	%
1 week	10	15
2 weeks	26	38
3 weeks	18	26
4 weeks	8	12
2 to 4 months	3	4
4 to 12 months	3	4

Symptoms attributable to lymphocysts do not become evident clinically until the usual postoperative discomfort has subsided. Table IV lists the cases in this series in terms of the time elapsed between surgical operation and diagnosis. It is notable that 54 of the 68 cases were diagnosed by the third postoperative week. A complaint of lower abdominal fullness or swelling, localizing lateral to the operative incision, is often the first indication of lymphocyst formation. As the size of the lymphocyst or lymphocysts increases, there is a growing prominence of one or both lower abdominal quadrants. The swelling is elliptical in form and roughly parallels the inguinal ligaments.

Urinary frequency and/or constipation are frequent and, with ambulation, the patient may favor a stooped position as the result of pain upon extension of the leg. Edema of the mons pubis, labia, and one or both lower extremities is not uncommon.

While the presence of a cystic mass can be readily confirmed by bimanual examination, the actual extent and significance of the collections can best be appreciated by radiographic methods. Plain film examination alone is not reliable since the normal pelvic soft tissue shadows have been obliterated or distorted by the preceding lymphadenectomy and only the presence of relatively large lymphocysts can be appreciated without use of contrast media.

Fig. 2.—Massive lymphocyst indenting the bladder and displacing, but not obstructing, the left ureter. The lateral arrows indicate the periphery of the cyst; the medial, the displaced ureter. The patient had few complaints.

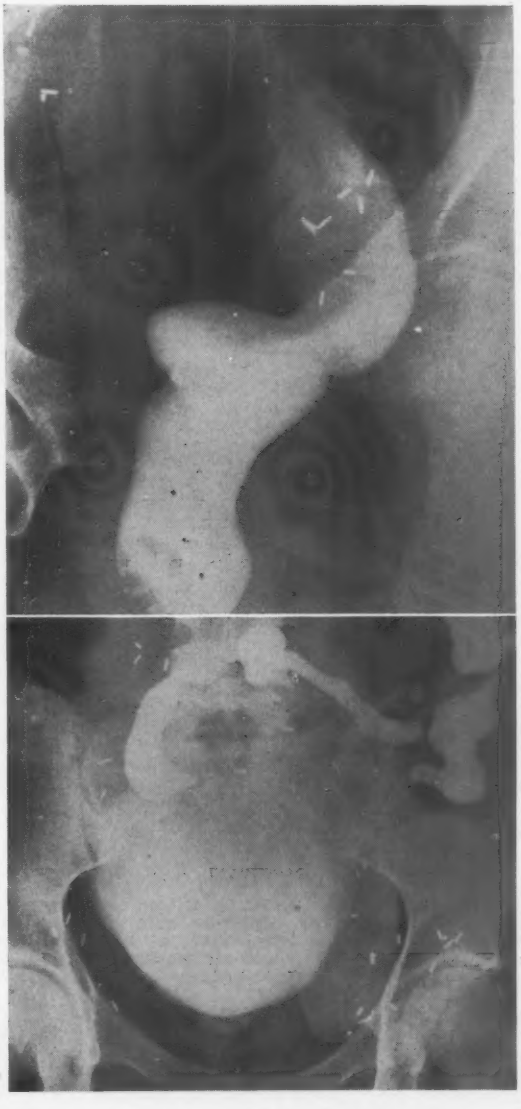
The effects upon the urinary tract and colon, however, are readily demonstrated by pyelographic and barium enema examinations. Compression of the urinary bladder is commonplace and productive of frequency (Figs. 2 and 5). Similarly, displacement and compression of the sigmoid cause a sensation of fullness which the patient frequently describes as "constipation." With the larger lymphocysts an actual effective obstruction may occur (Fig. 3).

The fluid content of the lymphocyst is under pressure and, depending upon the location, may compress the iliac veins against the pelvic wall and thus interfere with venous return (Fig. 4, *A*). An obstructive uropathy may be produced in a similar fashion or, if the lymphocyst is high on the pelvic wall, the ureter may be lifted medially and incorporated in the cyst wall

where it is both compressed and kinked (Fig. 4, *B*). Venography is not necessary to demonstrate obstruction of the pelvic veins since the edema of the lower extremities is ample evidence that obstruction is present.

Obviously the actual size and location of a lymphocyst can only be inferred by the pressure effects upon adjacent organs. Direct visualization

A.



B.

Fig. 3.—Obstruction of sigmoid by massive lymphocyst. *A*, Complete obstruction of retrograde flow of barium by extrinsic mass. Patient 4 months after irradiation; 2.5 months after operation. *B*, Direct opacification of the lymphocyst following removal of 1,500 c.c. of fluid. Note the compartmentalization of the cyst and the displacement and partial obstruction of the sigmoid colon.

requires injection of opaque material into the lymphocyst cavities following aspiration of the fluid content (Figs. 1, *A* and 3, *B*). If desired, carbon dioxide or nitrous oxide may be substituted for the radiopaque dyes. Such

procedures are of academic interest only. The effects upon the intrapelvic structures are of paramount importance and can be ascertained by the conventional methods described without the risk of infection incurred by the use of direct opacification techniques.

While the initial symptoms are distressing and appreciably prolong postoperative morbidity, the late effects or complications are most important from the standpoint of survival. Among these are obstructive uropathy with uremia, bowel obstruction, fistula formation, and infection of the lymphocyst.

A. *B.*

Fig. 4.—Bilateral lymphocysts producing obstruction of the ureter and pelvic veins. *A*, Venogram performed May 4, 1956. There is obstruction of the left external iliac vein with extensive filling of the collateral channels. A bilateral hydronephrosis was present and the left leg was markedly edematous. *B*, Intravenous pyelogram performed Nov. 6, 1956. The soft tissue mass representative of the lymphocyst is displacing and obstructing the right ureter. The left urinary tract and lower extremity were normal at the time. Complete bilateral regression eventually occurred with conservative management.

The more common differential diagnoses are those of urinary retention, cystitis, hematoma, infection of the incision, and thrombophlebitis. The small percentage of lymphocysts that inexplicably appear late in the postoperative phase may be confused with recurrent carcinoma.

Treatment of the Lymphocysts

If there is no demand for immediate treatment, the lymphocysts should be observed for spontaneous regression. This is usually possible with the smaller ones. Regression is often slow and extends over a period of several months (Fig. 4). For the large and more incapacitating lymphocysts, immediate though temporary relief can be obtained by aspirating the fluid. The needle puncture may be made through either the abdominal or vaginal

walls. The more prominent part of the mass is chosen for puncture and this can be determined by abdominal and vaginal palpation. Since refilling usually occurs in 24 to 36 hours, multiple taps are necessary. This almost invariably causes secondary infection (Fig. 5). Strict sterile technique should always be observed when an aspiration is performed on these patients.

The lymphocysts that become infected may grow into a large abscess which is too deep to develop its own drainage to the outside. In these circumstances incision and drainage are advised. The approach to incising the lymphocysts has been most frequently through the lower abdominal wall; however, in several patients the lymphocysts could be felt prominently through the vagina. Incision by this route leads to rapid recovery because of the excellent dependent drainage.

Lymphocysts that obstruct the ureter may damage the kidney if not relieved. This is a serious situation if the obstructed urinary tract is also infected. Conservatism is no longer possible and early incision and drainage are advised.

Fig. 5.—Bilateral lymphocyst with secondary infection following drainage. Gas shadows in left pelvis stem from dissection of air along fistulous tract. The opacified bladder is markedly compressed and the normal pelvic soft tissue shadows are obliterated.

Efforts to develop a method of prevention have not been wholly successful. As mentioned later, leaving the pelvic peritoneum open, with free connection between the dissection site and the abdominal cavity, was not effective.

We agree with Gray and associates that drains placed down to the dissection site at completion of the operation do not prevent lymphocyst formation. Such drains, even when placed on continuous suction for 2 to 4 days, seem to increase the incidence of lymphocyst formation. It seems reasonable to make an effort to ligate those large lymphatic channels that are encountered during the dissection. Near the entrance to the femoral canal and along the obturator nerve near its exit, large lymph vessels can often be identified and ligated.

In approximately one half of the patients, we have used trypsin, 5 mg., intramuscularly twice daily for 5 to 8 days. Trypsin is freshly prepared by dissolving the powdered form in a gelatin base.* The injections are given in the gluteal muscle, starting the day before or immediately following operation. As shown in Table V, the use of this drug has not reduced the incidence of lymphocysts, but their average size was reduced as noted in Table VI. Since the severity of this complication is primarily a function of size of the lymphocysts apparently we have obtained considerable help from the use of this drug. A larger series of patients will be studied to evaluate its effect more accurately.

TABLE V. THE EFFECT OF TRYPSIN ON LYMPHOCYST FORMATION

	TOTAL NO. OF CASES	NO LYMPHOCYST FORMATION	LYMPHOCYST FORMATION
No trypsin	184	146 (79%)	38 (21%)
Trypsin	97	67 (69%)	30 (31%)

TABLE VI. THE SIZE OF LYMPHOCYSTS IN RELATION TO THE USE OF TRYPSIN

	TOTAL CASES WITH LYMPHOCYSTS	SMALL	MEDIUM	LARGE
No trypsin	38	20 (53%)	8 (21%)	10 (26%)
With trypsin	30	24 (80%)	3 (10%)	3 (10%)

Comment

Gray and co-workers have suggested that prior irradiation of the pelvis is an important factor in lymphocyst formation. Yet their incidence of 16.4 per cent (55 patients) is considerably less than in Mori's series of patients that did not receive preoperative irradiation. The incidence in the latter group was 47 per cent (121 patients) as compared with 58 per cent (19 patients) who received preoperative radiation therapy. This increase of 11 per cent is probably not significant because of the small number of patients in the irradiated group.

It is difficult to draw any conclusions on this irradiation question from our material. The patients who received no significant irradiation to the dissection site had a low incidence of lymphocysts but the same group also had a concurrent hysterectomy.

Most of the remaining patients had lymphadenectomy without hysterectomy after irradiation. Those treated with supervoltage methods had a tumor dose to the pelvic and para-aortic nodes in the range of 6,000 to 7,000 r. Patients treated with orthovoltage equipment received approximately 20 per cent less. In Table VII, the equal incidence of lymphocyst formation for the two methods would suggest that irradiation, if a contributing factor, provides a threshold dose in the range of the orthovoltage media.

There is no one factor that has been found to be responsible for the formation of lymphocysts. We cannot explain why 24 per cent of the post-lymphadenectomy patients are unable to dispose of this fluid. There must be some special factor responsible for certainly in all patients the operation disrupts at least to some degree the lymphatic drainage from the respective sides of the pelvis and lower extremities. The lymph fluid must continue to pour from the open lymph vessels. This can be demonstrated by the fact that constant suction tubes to the dissection site will remove 200 to 300 c.c. of fluid per day for a period of 3 to 5 days. Probably in all cases then there

*Supplied as Parenzyme through the courtesy of Research Laboratories of The National Drug Company, Philadelphia, Pa.

is sufficient fluid deposited in the area during the first few days following the operation to fill a lymphocyst. Why this fluid does not cause symptoms in more patients and why the symptoms do not appear more promptly postoperatively is not understood. It is possible that the loose flaps of the pelvic peritoneum will accommodate a large volume of fluid under low pressure until scar tissue contracts these tissues in an effort to obliterate the defect created by the operation. Thus, the fluid becomes confined to a smaller volume and is consequently under greater pressure. The force exerted on the surrounding structures then becomes apparent.

If the openings in the peritoneum become sealed early or the collateral flow is delayed, lymphocysts develop. In a small series of patients we deliberately did not suture the margins of pelvic peritoneum, but there was no reduction in the lymphocyst formation. In patients in whom only one side was reperitonized, bilateral lymphocysts still developed. A theoretical function of trypsin is to establish collateral channels for the lymph flow before a cyst wall is formed by scar tissue.

In lymphocysts the fluid content is apparently not static. If aspirated, the space will refill. If radiopaque material or dye is placed in the enclosed space, both will disappear. It has been suggested that the lymphocyst is a reservoir with a steady stream of fluid passing through the space. This is supported by the observation that if chemical dye is placed in the corresponding lower extremity, the dye can be recovered from the lymphocyst fluid.

The left side has been reported[2] to be the side most commonly involved. Table VIII shows that bilateral involvement was almost twice as frequent as unilateral. Clinically there was no significant difference in the severity of the problem on either side of the pelvis.

TABLE VII. LYMPHOCYST FORMATION ACCORDING TO IRRADIATION TREATMENT

METHOD OF TREATMENT	TOTAL NUMBER OF CASES	LYMPHOCYST FORMATION	%
Betatron	167	49	29
250 kv.	50	12	24
Local radium only	61	4	7

TABLE VIII. LOCATION OF LYMPHOCYSTS

LOCATION	NUMBER	%
Bilateral	33	49
Left side	20	29
Right side	15	22
Total	68	

Summary

Lymphocysts developed in 68 of 281 patients following pelvic lymphadenectomy, an incidence of 24 per cent. This is the second report in the American literature of this complication in a large series of cases.

The statistical relationship of the incidence of lymphocyst formation to the stage of the carcinoma, preoperative irradiation, and metastases to the regional lymph nodes is presented. No one factor can be isolated as the causative agent at the present time. Methods of diagnosis, prevention, and treatment are discussed.

The significance of this problem is reflected in the prolonged postoperative disability that follows this complication.

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Discussion

DR. JOHN J. McDONOUGH, Youngstown, Ohio.—Dr. Rutledge has called our attention to a serious complication of lymphadenectomy in the treatment of carcinoma of the uterus. He rightfully asks, "Why has so little been written concerning the distressing complication of lymphocyst following lymphadenectomy?" Why, indeed! The operation has been rather extensively performed in our country for the past 10 to 12 years, yet no reports, save one by Gray, have appeared in the American literature.

Nobuo Mori, who has extensively reviewed the Japanese literature and who reports a personal series of 140 cases, found the incidence of lymphocyst formation to be 48.5 per cent after the Okabayashi operation. He is convinced that the occurrence of lymphocyst will depend directly on the radical extent of the pelvic lymph node dissection. He believes that formation of a lymphocyst is inevitable in a substantial number of cases following a properly performed lymphadenectomy. No way has been found to prevent the formation of the encysted lymph accumulation and he treats his patients expectantly and conservatively. Surgical drainage is practiced when large lymph accumulations occur. He does not believe that this complication effects the prognosis of malignant disease of the uterus.

Gray, Plentl, and Taylor, reporting in the May, 1958, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, list a minimum lymphocyst incidence of 16 per cent with one death and one additional operation in 6 of 9 patients who had a lymphocyst complication. According to Gray, the technique of lymphadenectomy did not appear to influence lymphocyst formation. The complication followed the retroperitoneal, as well as the transperitoneal, approach to the pelvic lymph nodes.

Gray further states that since lymphocyst formation constituted such a large proportion of morbidity and mortality the operation of lymphadenectomy, as a routine procedure following maximum radiation therapy for carcinoma of the cervix, has been abandoned at the Sloane Hospital for Women and the Frances Delafield Hospital.

Frankly, this problem puzzles me. I have been performing the operation of radical hysterectomy with bilateral lymph node dissection since 1946, and I have not seen, or at least I have not recognized, the complication of lymphocyst in my work. In a small personal series of cases this complication may possibly have been overlooked. Still, if the incidence of lymphocyst formation is roughly 25 per cent, I should have encountered the problem at least 10 to 15 times. Any complication with this frequency would be well known to me and better known to many others. Moreover, it should have been frequently reported, especially from the larger centers.

Failure to recognize and diagnose this complication of radical pelvic surgery is certainly one reason for our lack of knowledge about it. Healing following radical surgical procedures is necessarily long and drawn out at times, and discomfort to the patient beyond the normal recovery time is not unusual nor unexpected. I can remember one case following a radical hysterectomy with bilateral lymph node dissection in which the patient had pain and discomfort on the right side for 10 weeks postoperatively and I could find no reason for the discomfort. She preferred to walk slightly bent over and to the affected side for relief. She has since recovered, but did she have a lymphocyst?

Second, perhaps dissection of the pelvic lymph nodes is often selective rather than complete even though I am sure the aim in most lymphadenectomies is to be as thorough as possible. It appears that if only a few pelvic lymph nodes are removed (rather than all or most of these structures) lymphocyst will not occur.

A critical survey of Dr. Rutledge's paper and the literature on lymphocyst formation leads to the following tentative conclusions:

1. The incidence of lymphocyst formation is in direct proportion to the extent of the pelvic dissection. Percentagewise, the actual incidence appears to run roughly between 15 and 50 per cent depending upon the experience of the operator.

2. The greater the number of pelvic nodes removed, the higher the incidence of lymphocyst formation.

3. The greater the number of cancer-positive nodes removed in performing a lymphadenectomy, the greater the incidence of lymphocyst formation.

4. It is possible that the incidence of lymphocyst formation is substantially higher when lymphadenectomy follows complete radiation therapy than it is following primary radical hysterectomy with bilateral node dissection, yet there are no comparative studies to support this conclusion.

Regarding treatment, I am disappointed that Dr. Rutledge has found no uniformly successful remedy for this complication. That continuous suction drainage has not helped the condition is at first surprising. This latter method of drainage has been a boon to me in radical groin and breast dissections and allows primary wound healing in many cases. In the breast and groin, however, it is possible that we are dealing with a large volume of serosanguineous drainage and a small amount of lymph. In the pelvis there is a greater amount of lymph and in this instance perhaps continuous suction drainage is the wrong approach and may only delay the time when the tissue of the pelvis would normally take over the absorption of lymph.

Thus the administration of trypsin, as Dr. Rutledge points out, with its action of mobilization of tissue fluids, seems to be a logical method of treatment. So far it has been most helpful to him.

Surgical drainage of the cysts where required is understood, yet it is good that in general an over-all conservative regime is best. It is apparent that this has helped me and perhaps others over this complication when the lymphocyst was small and unrecognized.

Further study by other members of this organization might profitably be given to the problem of lymphocyst formation. It should be distinctly helpful to us and to our patients in the evaluation of pelvic lymphadenectomy.

ABRUPTIO PLACENTAE*

A Ten-Year Survey

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ONE of the major concerns in the management of a large indigent maternity service is the frequency with which one encounters serious abruptio placentae. With this condition is imposed a constant maternal risk with almost inevitable fetal compromise. Its recognition, then, and prompt treatment become necessary in order to avoid tragic fetal and maternal deaths.

The important effects of placental separation as far as the mother is concerned were outlined by Page and associates[1] in 1954. These hold valid today and are as follows: "(1) a degree of shock which is frequently out of proportion to the hypotension, (2) a disseminated 'fibrin embolism,' (3) an in vivo defibrination resulting sometimes in an incoagulable blood, (4) an ischemia of the renal cortex which leads to varying degrees of necrosis, and (5) the activation of the fibrinolytic system in the plasma." He further postulated that it was very possible that an infusion of biologically active materials from the separation site into the maternal circulation is responsible for all five events.

Historically, DeLee[2] called attention to a bleeding diathesis in this condition in 1901 and Dieckmann[3] reported very low levels of fibrinogen in severe cases of abruptio placentae in 1936. The mechanism for these events may be due to varying degrees of liberation of thromboplastin into the maternal circulation from the placental site, perhaps by autolysis of the decidua, aided by exaggerated intrauterine pressure, the last a concept of Weiner and coworkers.[4]

That this condition has been a constant source of maternal deaths for many years in the past is cryptically stated in repeated entries in the old anesthesia records at Charity Hospital in New Orleans. One will find this type of entry: "Diagnosis: abruptio placentae—Result: death—Cause of death: *bleeding diathesis.*" Since many patients did not receive an anesthetic

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and therefore failed to become an "entry," one can only guess what the probable high incidence of maternal deaths must have been from abruptio placentae alone!

We have come to believe that emphasis must be placed on the alert recognition of this condition and, in our experience, on the speed with which the processes concerned with it can be arrested. A diagnosis of the condition, its progress, and its severity is all-important in deciding the type of treatment indicated and its urgency. We have been able to accomplish this by constantly maintaining a high index of suspicion.

Our clinical observations have supported repeated evidence that the syndrome of the placental separation is a progressive event. If observed in its entirety, it must begin with a degree of placental separation following which mild uterine tetany will ensue. Early fetal distress may be observed. As the process continues there may be uterine pain, increased uterine tetany, and definite evidence of fetal distress. Again, external bleeding may be absent. Finally, maternal shock accompanied by a recognizable bleeding tendency due to lowered blood fibrinogen develops. The fetus is usually dead and at this stage the mother's life may be in jeopardy.

It is well to realize that although these events may occur over a long period of time and the process may never advance from the mild stage, there may be a rapid progression precipitately catapulting the mother into severe shock in a relatively short period of time.

The diagnosis begins with an attitude of suspicion wherein one searches for uterine changes, fetal distress, and vaginal bleeding. All these are frequently associated with hypertension at the present moment but not necessarily historically. Frequent observation of the peripheral blood for signs of blood loss or a clotting defect is necessary. Where facilities for obtaining fibrinogen blood levels are unavailable, observation of clot formation in a test tube is reliable. Finally, watchfulness for worsening of symptoms is mandatory.

In this report we are concerned with the *severe* types of abruptio placentae and the rationale for our present concepts of management. All of the patients herein described were indigent and were admitted to the Tulane Obstetrical Unit at the Charity Hospital in New Orleans. All were known to the senior author. In many instances the women described had traveled up to 150 miles to reach the hospital, and had often developed the entity at home and were compromised by a serious delay of several hours. Many were admitted in shock.

Materials

The patients studied were admitted to the Tulane service over a 10 year period, Jan. 1, 1946, to Dec. 31, 1955. During this period, 39,076 women were delivered on our service. This, incidentally, accounts for approximately 40 per cent of the over 90,000 deliveries that occurred in the hospital during the same time. There were 82 serious cases of abruptio placentae in the first 5 years and 132 in the second, a total of 214 with an over-all incidence of 0.54 per cent (Table I).

Although the methods for diagnosis have been constant, no analytical explanation was found to interpret the increased incidence during the second

5 year period. For the past 8 years a constant incidence of approximately 6 per 1,000 deliveries of all types has been observed. Of the patients presented, 84 per cent were Negro. Their ages ranged from 17 to 45 years with the greatest number (105 patients) in the 21- to 30-year-old group (Table II). Thirty-three were primigravidas and 181 multigravidas and, of the latter, 75 had had 5 or more pregnancies.

TABLE I. FREQUENCY OF ABRUPTIO PLACENTAE

YEARS	NO. PATIENTS	TOTAL DELIVERIES	%
1946-1950	82	17,414	0.46
1951-1955	132	21,662	0.61
Total	214	39,076	0.54

TABLE II. AGE INCIDENCE

AGE	NO.
20 or less	39
21-30	105
31-40	65
41-50	5
Total	214

Etiological Factors.—No *constant* contributing factors in the production of serious placental separation were found. Over half (127) had attended the prenatal clinic, yet only 17 were known to have had hypertension, 28 pre-eclampsia, 2 previous placental separation, and none eclampsia with past pregnancies (Table III). Multiparity and the indigent status of the women were the only impressive statistical constants in establishing common ground for the high rate of placental separation in them as compared to our experiences in private practice. In no instance was trauma considered to be a contributing factor in spite of the relative frequency of admissions following automobile accidents and severe injuries involving pregnant women.

TABLE III. ETIOLOGICAL FACTORS

Antenatal Care.—	
Attended clinic	127
No clinic visit	87
Previous History.—	
Hypertension	17
Pre-eclampsia	28
Eclampsia	0
Abruptio placentae	2

TABLE IV. SIGNS AND SYMPTOMS (214 PATIENTS)

Vaginal bleeding	168
Abdominal pain	103
Tetanic uterus	52
Albuminuria	66
None	35
Blood pressure 140/90 or less	134
Blood pressure over 140/90	80

Diagnosis.—Vaginal bleeding was present in 168 patients, abdominal pain in 103, a tetanic uterus in 52, and albuminuria in 66. Thirty-five women exhibited none of these signs or symptoms on admission (Table IV). A blood

pressure on admission of 140/90 or less was found in 134 women and 80 had pressures higher than 140/90. The hematocrit on admission was 41 per cent or above in 3 patients, between 30 and 40 per cent in 114, and below 30 per cent in 47. In the first 5 years of this study, hematocrit determinations were not performed routinely and were not obtained in 41 patients.

Of the associated conditions present, the following were noted: placenta previa 4, eclampsia 4, transverse lie 3, fetal monsters 3, ruptured marginal sinus 2, and compound presentation, amnionitis, circumvallate placenta, prolapsed cord, diabetes, and thyrotoxicosis, one each. Eighty patients had hypertension (Table V).

TABLE V. ASSOCIATED CONDITIONS

Placenta previa	4
Eclampsia*	4
Transverse lie	3
Fetal monsters	3
Ruptured marginal sinus	2
Compound presentation	1
Amnionitis	1
Circumvallate placenta	1
Prolapsed cord	1
Diabetes	1
Thyrotoxicosis	1
Hypertension	80

*Includes 2 deaths.

Delivery.—Of 133 patients delivered vaginally, 108 suffered incomplete placental separation (estimated to be 50 per cent or more) and 25, complete. Cesarean section was the method of delivery in 81 patients. Of this number, hysterectomy was indicated in 23. The cesarean section rate was 37.8 per cent (Table VI). The anesthetic of choice was general (inhalation) in 83 patients, local in 15, spinal in 5, and combined in 10. No anesthesia was required in 101 patients.

TABLE VI. MODE OF DELIVERY

TYPE OF DELIVERY	PARTIAL SEPARATION	COMPLETE SEPARATION	TOTAL
Vaginal	108	25	133
Cesarean section (rate 37.8%)	39	19	58
Section hysterectomy	5	18	23
Total	152	62	214

Fifty per cent of all patients required blood transfusions and one sixth of that group received 2,000 ml. or more.

TABLE VII. CLOTTING DEFECTS

TIME NOTED	NO. PATIENTS
At surgery	15
Before surgery	1
Total	16 (7.4%)

Afibrinogenemia.—A clotting defect (afibrinogenemia) was severe enough to require the administration of fibrinogen to 16 patients, 7.4 per cent (Table VII). The average amount administered was 2.6 Gm. The least dose was 1.0 Gm. and the maximum was 11.0 Gm., which was required to correct the

clotting defect. After closer scrutiny, it was felt that if fibrinogen had been readily available in the first 5 years (1946-1950) it would certainly have been used more freely. The present standard incidence of severe clotting defect is 10 per cent of all cases of abruptio placentae we observe.

Since it has been our policy to empty the uterus promptly whenever a massive placental separation was suspected and since this could not always be accomplished with facility and expediency from below the abdominal route was frequently utilized. The classical Couvelaire uterus was found in 41 women (20 per cent) (Table VIII). Of these, only 17 cases were considered severe enough to require hysterectomy and 2 uteri were removed after vaginal delivery because of uncontrollable uterine bleeding due to atony. It may be added that oxytocics had failed to evoke favorable response.

TABLE VIII. MANIFESTATIONS OF COUVELAIRE UTERUS

Myometrial infiltration	8*	
Myometrial and subserosal	11	
Myometrial and subserosal with extension to broad ligament	22†	
Total	41	(20%)

*2 required hysterectomy.
†15 required hysterectomy, 2 after vaginal delivery.

Two patients received intra-arterial transfusion and we feel this was responsible for their recovery. In each, peripheral vascular collapse thwarted all efforts to use the conventional methods of blood administration. This has been reported previously by Collins and associates.[5]

Complications.—The complications following all deliveries are listed in Table IX. The most common were pyelitis, endometritis, uterine atony, and pneumonia-atelectasis. The over-all morbidity was 22.4 per cent.

TABLE IX. POSTPARTUM COMPLICATIONS

Pyelitis	15
Endometritis	7
Postpartum uterine atony	5
Pneumonia-atelectasis	5
Phlebitis	3
Wound separation	4
Allergic blood reaction	2
Incorrectly cross-matched blood	1
Homologous serum jaundice	1
Vaginal cuff hematoma	1
Cholecystitis	1
Wound abscess	1
Intestinal obstruction	1
Ileus	1
Parametritis	1
Bilateral retinal detachment	1

Morbidity: 48 patients (22.4%).

Urinary Suppression.—Since persistent anuria or severe oliguria will follow periods of shock requiring transfusion and also can be expected when afibrinogenemia develops, this complication caused concern whenever observed. Anuria was frequently observed during the first 48 hours but was present for a longer period in 5 patients. One of these died. Severe oliguria was present in 3, one of whom died. As will be shown, renal cortical necrosis was present in 3 patients and tubular necrosis of the kidneys in one. These complications were represented in 4 of the 6 patients who died.

TABLE X. MATERNAL DEATHS

NO.	GRAVIDA	CLINIC PATIENT	BLOOD PRESSURE ON ADMISSION	DURATION OF SYMPTOMS: PRIOR TO ADMISSION (HOURS)	DURATION OF SYMPTOMS: FROM ADMISSION TO DELIVERY (HOURS)	CAUSE OF DEATH
1	vi	No	218/120	3 to 6	2	Renal cortical necrosis
2	x	No	0/0	8	Immediate	Shock
3	x	Yes	50/40	3	Immediate	Tubular necrosis of kidneys
4*	i	No	170/130	1	29	Cerebral thrombosis
5	vii	No	170/120	6	Immediate	Renal cortical necrosis
6*	viii	Yes	170/110	1	24	Renal cortical necrosis

*Had eclampsia.

Maternal Deaths

There were 6 maternal deaths, 3 occurring in each 5 year period (Table X). They are summarized below:

CASE 1.—April 13, 1949. E. B., aged 37, gravida vi, para iii, a nonclinic patient, 7 months pregnant, was admitted with symptoms of scotomas, edema, and abdominal pain. She had had symptoms for 3 hours. The uterus was tetanic, and fetal heart tones absent; the cervix was long and closed. The hematocrit was 18, blood pressure 218/120, and albuminuria, 4 plus. A stillborn premature infant was delivered by cesarean section and 1,000 c.c. of blood was found in the uterus. The placenta had completely separated. A transfusion of 2,000 c.c. whole blood given. Anuria developed for 24 hours and the patient died on the seventh postoperative day. Autopsy findings: bilateral renal cortical necrosis.

Comment.—This represents the sequelae of shock in severe abruptio placentae and the kidney lesion often observed. Delay in admission was considered contributory.

CASE 2.—Dec. 17, 1949. E. J., aged 35, gravida x, para ix, was 8 months pregnant and had not visited the clinic for 2 months. She traveled 60 miles to the hospital after the placenta separated at home approximately 8 hours before. She was in shock on admission and no blood pressure or pulse was recorded. Blood, 2,000 c.c., was administered rapidly and a classical cesarean section was performed. The placenta was completely separated and 1,500 c.c. of blood was found in the uterus. The fetus was dead. The patient failed to respond at any time and died at the end of the procedure, 70 minutes after admission. No autopsy was performed.

Comment.—It is doubtful that any procedure would have saved this woman. Again, the delay increased the serious involvement and jeopardized the life of both mother and baby.

CASE 3.—Aug. 22, 1950. L. E., aged 29, gravida x, para ix, a clinic patient, was admitted at term after 3 hours of bleeding. There was low abdominal pain, a tetanic uterus, and no fetal heart tones. The blood pressure was 50/40; the cervix was 2 cm. dilated and 40 per cent effaced. Blood was administered and a cesarean section performed. A 6 pound stillborn infant was delivered, and an estimated 3,000 c.c. of blood was found in the uterus. There was myometrial extravasation of blood which extended into the broad ligaments. A hysterectomy was performed. In spite of a 5,500 c.c. blood transfusion, the blood pressure failed to rise over 80 mm. Hg. She died 12 hours after admission. Autopsy findings: myocardial fragmentations, liver necrosis, tubular necrosis of both kidneys, and pulmonary congestion.

Comment.—Massive abruptio placentae with delay occasioned the progressive symptoms. In view of present-day knowledge, fibrinogen, had it been available, might have made a difference in combating the shock since similarly stricken women have been known to overcome a kidney lesion like the one present at the death of this patient.

CASE 4.—April 18, 1951. B. K., aged 20, gravida i, para 0, a nonclinic patient, 7 months pregnant, was admitted with eclampsia and in a coma. She had had convulsions at

home. The blood pressure was 170/130, and albuminuria, 4 plus; there was no external bleeding. Treatment of the eclampsia was instituted. Because the cervix remained firm and closed and because the baby was dead, we elected to "watch" her. At the end of 29 hours, it was decided to empty the uterus since there had been no change in the condition of the cervix. When the uterus was incised, blood literally "hit the ceiling" of the operating room. A 100 per cent placental separation was found and a dead macerated fetus was delivered. There was massive subserosal extravasation of blood in the myometrium and into both broad ligaments. The uterus was removed. The patient improved and responded. On the twenty-second postoperative day, she had convulsions and died. No autopsy was performed but cerebral thrombosis was suspected.

Comment.—In the light of present-day knowledge, we take responsibility for this death since we feel that this patient was inadvertently compromised by a 29 hour delay in action.

CASE 5.—June 2, 1954. L. J., aged 36, gravida vii, para iii, was 7 months pregnant. This nonclinic patient had suffered a placental separation with her previous pregnancy. She was admitted after having bled at home for 6 hours. The blood pressure was 170/120, the uterus was tetanic, and no fetal heart tones could be heard. Hemoptysis was noticed. After 15 minutes of a Pitocin drip, she was delivered of a 3 pound stillborn fetus. Oliguria developed, then diuresis. She died on the tenth day. Autopsy findings: bilateral renal cortical necrosis.

Comment.—We again feel that delay in active treatment was responsible to a great extent for this maternal death.

CASE 6.—Oct. 17, 1954. L. A., aged 32, gravida viii, para vi, a clinic patient known to be pre-eclamptic was admitted at term following eclamptic convulsions at home. Her blood pressure was 170/110. Twenty-four hours after admission, because of an unprepared cervix and the fact that the fetus was alive, a cesarean section was performed. There was evidence of at least 50 per cent placental separation (silent) and extravasation of blood in both the myometrium and subserosally. Blood, 1,500 c.c., was administered together with 2 units of fibrinogen. An 8 pound, 6½ ounce infant survived. The patient remained oliguric until death on the third postoperative day. Autopsy findings: multiple infarction of the liver, pulmonary edema, glomerulonephritis, lower nephron nephrosis, hemorrhage in the pituitary, and renal cortical necrosis.

Comment.—This silent placental separation defied detection and, no doubt, was overshadowed by the eclampsia and its therapy. The high incidence of placental separation in eclampsia should always evoke searching suspicion. In retrospect, it is doubtful that we could have managed this patient's disease in any other fashion.

Comment

It would appear, from these maternal death summaries, that a number of factors contributed to the end result. Only one patient was a primigravida (5 had had 6 or more pregnancies), 2 had eclampsia, and only 2 had attended the prenatal clinic. Parity, then, and the lack of prenatal care, set the stage as it were. Eclampsia and toxemia as well contributed. However, even when these hazards were known to be present, the one impressive common denominator was time. It is impressive that in each of the maternal deaths there was a delay of from 3 to 29 hours from the time of actual separation of the placenta until delivery. In retrospect, delay in active treatment seemed to be the all-important factor.

As was demonstrated, the cause of death was proved by necropsy to have been renal in 4 out of 6 women (66 per cent). If the etiology of renal damage is conceded to be hypoxia accompanying shock, ischemia of the renal cortex producing necrosis, and/or fibrin emboli, the prompt resolution of a process as insidious and progressive as abruptio placentae is mandatory. By virtue

of these experiences we have learned that delivery should be accomplished as early as possible when this entity is strongly suspected or is recognized. Whole blood and fibrinogen are both indispensable.

It was learned from this study that if delivery was accomplished in less than 2 hours after recognition of the separation, the fetal salvage was 50 per cent by vaginal delivery and 21 per cent by abdominal delivery, a combined loss of 62 per cent (Table XI). If delivery was delayed 2 to 12 hours, the vaginal delivery salvage was 22 per cent, and by cesarean section, 30 per cent, a combined loss of 75 per cent. If the delay was extended from 12 to 72 hours, the fetal salvage by vaginal delivery was 34 per cent, and by cesarean section, none, a combined fetal loss of 71 per cent. Thus, the over-all picture revealed a fetal salvage of 49 per cent by vaginal delivery and only 21 per cent by cesarean section.

TABLE XI. FETAL MORTALITY BY METHOD OF DELIVERY

HOURS BETWEEN RECOGNITION AND DELIVERY	VAGINAL DELIVERY				CESAREAN SECTION				TOTAL DELIVERIES	FETAL MORTALITY (%)
	ALIVE	DEAD	TOTAL	%	ALIVE	DEAD	TOTAL	%		
Less than 2	45	45	90	50	13	51	64	79	154	62
2 to 12	8	29	37	78	55	11	16	70	53	75
12 to 72	2	4	6	66	0	1	1	100	7	71

In this respect, the use of cesarean section, though admittedly giving poor results in reference to the fetus, has a real place in this condition since we feel that the strong *maternal* indication warrants its free use in the interest of time. Once the decision has been made to empty the uterus promptly, cesarean section should be utilized whenever delivery cannot be accomplished in haste and with facility from below. The impetus is enhanced in the presence of a dead fetus. These views are supported by those who have had like experience[6-15] (Table XII). That the reported rate for cesarean section in abruptio placentae varies from zero to 37 per cent is thought to be due not to marked difference in philosophy of management, but rather to the *type* of patient one encounters and the definition of the entity itself in the patients studied.

TABLE XII. USE OF CESAREAN SECTION IN ABRUPTIO PLACENTAE

	NO. CASES	CESAREAN SECTION (%)	MATERNAL DEATHS (WHOLE SERIES)
Schroeder[6]	117	0	3
Ferguson[7]	195	2	0
Hester and Salley[8]	100	3	4
Taylor and Hangen[9]	70	6	0
Daro and associates[10]	306	12.1	6
Waddington[11]	254	18	1
Posner[12]	82	28.1	3
Gabriels[13]	108	35	1
Dyer and McCaughey	214	37	6

When a patient is admitted to our obstetrical unit with suspected abruptio placentae, blood is drawn immediately for peripheral blood studies and a test for clot formation. At least 1,500 c.c. of whole blood is made available at once and a sterile vaginal examination is performed. Not only are other causes for bleeding eliminated but, most important, the status of the cervix

and the feasibility of vaginal delivery are ascertained. If indicated, amniotomy is performed and oxytocic stimulation instituted, the objective being to empty the uterus promptly. Should this not be deemed possible, we resort freely to abdominal delivery. It is agreed that the Couvelaire uterus is less of a threat since fibrinogen has become available; hence, hysterectomy is much less frequently performed. With this line of attack, there has not been a maternal death from abruptio placentae since October, 1954, though the incidence remains the same, about 1:180 deliveries. We have reduced the need for fibrinogen since the syndrome accompanying abruptio placentae is interrupted before a serious clotting defect can develop.

Summary

1. Two hundred fourteen cases of severe abruptio placentae are presented. These occurred over a 10 year period.

2. Only severe placental separations are considered (50 per cent or more separation).

3. The incidence is about 1:180 deliveries or 6 per 1,000 and is more common in multigravidas.

4. No constant etiological factor was demonstrated; however, one should have a high index of suspicion when treating the indigent, nonclinic, hypertensive, and toxic patient.

5. Cesarean section is employed freely to empty the uterus whenever vaginal delivery cannot be accomplished promptly.

6. The regimen presented has markedly reduced maternal deaths in our experience.

Conclusion

Abruptio placentae must be considered a serious condition. Once it is established, it is a progressive, vicious entity which, by chain reaction, sets off a recognizable syndrome, the extent of which is often in direct proportion to the period of time the condition is allowed to remain and this is further mirrored by the serious sequelae in the host.

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Discussion

DR. ALWYN E. BENNETT, Cleveland, Ohio.—At Cuyahoga County Hospital we have noted that complications occur at least 3 times more frequently in the patients who had no care and twice as frequently in the patients who have received inadequate care than in the patients who have received adequate care. The authors report that 22 per cent of the 127 patients who attended the prenatal clinic had a history of elevated blood pressure or toxemia with previous pregnancies and that 80, or 37 per cent, of their 214 patients had blood pressures above 140/90. May not a considerable number of the remainder have had blood pressures in the so-called high normal range, or other evidences of toxemia during their pregnancy?

The authors point out that 106 of the 214 patients required blood transfusions and 22, or 21 per cent, of these required 2,000 c.c. or more of blood. In this group of patients mention should be made of the possible need for calcium to prevent calcium depletion, gamma globulin to prevent hepatitis or homologous serum jaundice, and fibrinogen if any clotting defects are evident or if there is a level of fibrinogen below 100.

They also report that 41, or 20 per cent, of their patients had a Couvelaire uterus and in this group the availability of calcium, gamma globulin, and fibrinogen in addition to blood becomes very important.

Anuria persisting over 48 hours, as occurred in 5 of the patients, may involve a possible need for an artificial kidney, especially if there is a rise in potassium above 6 mg. or definite changes in the ECG of the patient. The fetal mortality of 51 per cent by vaginal delivery and 79 per cent by cesarean section or an over-all loss of 62 per cent is due, I think, not so much to the method of delivery as to the severity of the disease. The authors point out that the shorter the duration of the disease, the greater was the fetal salvage.

There were 6 maternal deaths. Four of these patients had no prenatal care, a fifth patient had been bleding for 3 hours before admission and the sixth patient was eclamptic. Four of these patients had high blood pressure and toxemic. It sems possible, in view of the blood loss sustained by the other 2, even though the blood pressure of one was 0/0 and the other was 50/40 on arrival at the hospital, that these patients were also toxemic.

I would like to present some data to indicate what is going on in 2 Cleveland hospitals. The statistics are taken from Cuyahoga County Hospital from July, 1954, through December, 1957, representing 11,169 deliveries, and from University Hospitals for the years 1956 and 1957, representing 8,414 deliveries, or a total in the 2 hospitals of 19,583 deliveries. There were 207 cases of placental separation at Cuyahoga County Hospital, of which 194 were partial and 13 were complete, and at University Hospitals there were 315 cases, of which 293 were partial and 22 were complete. In addition, at Cuyahoga County Hospital there were 47 patients with low implantation or marginal placenta previa. Two hundred and thirty-two of the 254 patients had live births and 22 had stillbirths at Cuyahoga County Hospital; 293 had live births and 22, stillbirths at University Hospitals. Of these, 317 were at term, 194 were premature, and 58 were immature. One hundred and thirty-six of the patients were primiparas and 433 were multiparas. The methods of delivery at Cuyahoga County Hospital were 103 spontaneous, 73 forceps, 28 breech, and 50 cesarean section. At University Hospitals 71 were spontaneous, 155 forceps, 14 breech, 1 version, and 57 cesarean section, or totals of: spontaneous 174, forceps 228, breech 42, version 1, and cesarean section 107. Seventy-five of these patients received blood transfusions and 5 had afibrinogenemia.

The percentage frequency of premature separation of the placenta, of different forms of delivery, of term, premature, and immature babies, and of the perinatal results is shown in Table I.

There were 2 deaths at Cuyahoga County Hospital and none at University Hospitals. The first death was in a 24-year-old Negro, gravida vii, para iv, at 36 weeks' gestation, admitted with a history of vaginal bleeding and abdominal pain. The uterus was tetanic

and tender and no fetal heartbeat was heard. A diagnosis of abruptio placentae was made. The blood pressure was 140/90; the cervix was firm and not dilated. Cesarean section under spinal anesthesia was started. When the blood pressure dropped, the patient was given 2 doses of a vasopressor drug. The blood pressure rose to above 300 and the patient complained of a severe headache, became unconscious, and died 8 hours later. Postmortem examination revealed massive cerebral hemorrhage.

TABLE I

	CUYAHOGA COUNTY HOSPITAL (%)		UNIVERSITY HOSPITALS (%)	
Premature separation	2.27		3.74	
Cesarean section	21.0		18.4	
Spontaneous delivery	40.0		26.3	
Forceps delivery	29.0		50.1	
Breech	10.0		5.0	
Term	47.2		62.5	
Premature	37.7		31.1	
Immature	14.6		6.3	
Stillbirths	8.6		6.0	
Live births	91.4		93.1	

The second death occurred in a 28-year-old gravida v, para iv, Negro woman at term. The cervix dilated from 2 cm. to full dilation in 65 minutes. Under Trilene, spontaneous delivery of a 5 pound, 2 ounce girl was effected in 68 minutes. The placenta was expelled in 9 minutes. The blood pressure dropped to 70 and examination showed cervical laceration which was repaired. Examination of the placenta showed there had been partial premature separation and it appeared likely that only the precipitate delivery had prevented this separation from becoming complete. Bleeding continued without clotting and 6 Gm. of fibrinogen was given. Bleeding continued; re-examination showed complete rupture of the left lateral wall of the lower uterine segment. Hysterectomy was performed and 1,000 c.c. of blood was found within the retroperitoneal space, with a tear in the left uterine artery and vein. Sixteen units of blood and 14 Gm. more of fibrinogen and repeated doses of calcium chloride were given, but the patient died 8 hours and 18 minutes after delivery.

The first case indicates the danger of vasopressor drugs in hypertensive patients and probably also an unwise choice of anethesia. The second case shows the importance of intrauterine examination in any patient with postpartum bleeding during or following the third stage of labor and the fallacy of assuming that cervical laceration ends in the vaginal vault.

LEIOMYOSARCOMA OF THE UTERUS*†

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LEIOMYOMAS, or fibroids, are among the commonest tumors encountered in human pathology, and the great majority of them affect the uterus. But, whereas the bulk of smooth-muscle tumors occurring in other locations are malignant (leiomyosarcomas), those springing from the uterine musculature are benign in more than 99 per cent of cases.

The first tumor described as a uterine sarcoma was presented before a meeting of the Berlin Obstetrical Society by Mayer[13] in 1859. His presentation was followed in later years by outstanding contributions by Williams,[31] Evans,[7] Novak and Anderson,[17] Finn,[8] MacFarlane,[12] and others.[6, 11, 18, 29, 30]

The problem of distinguishing benign from malignant myogenic neoplasms is difficult unless it is attacked critically. Benign metastasizing or recurring fibroids reported in the earlier literature[2, 10] were very likely examples of uterine leiomyosarcomas which had been sampled inadequately. On the other hand, cases of cellular degenerating fibroids and of stromal endometriosis have been "overdiagnosed" and placed in a malignant myogenic category.

It was accordingly considered worthwhile to present clinicopathologic and follow-up data on a personally studied series of 53 patients whose uterine leiomyosarcomas were observed at the Mayo Clinic in the 16 year period 1935 through 1950. During this same period, 26 cases of sarcoma of the endometrial stroma were encountered, as reported by Symmonds.[28]

Clinical Features

Age.—The ages of the patients at the time of diagnosis of the leiomyosarcomas ranged from 30 to 74 years with an average of 50.2 (Table I). Twenty-six patients were premenopausal while 27 were postmenopausal. None of the tumors appeared to have occurred prior to puberty.

Parity.—Parity varied from 0 to xii. Of 45 married patients, 12 were nulliparous.

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Past History.—In recent years, cases have been reported[8, 13, 20, 21, 23, 26] in which uterine sarcoma developed some years after irradiation for benign uterine bleeding. Nine of the 53 patients in this series gave a history of previous radium or roentgen therapy to the pelvic organs, presumably for benign disease.

It was assumed that leiomyosarcoma was present in 4 patients at the time of irradiation, since all noticed rapid progression of symptoms until their malignant disease was found after relatively short intervals (1 to 9 months). In 5 cases, periods of 14 months, 1½, 2½, 3½, and 6 years elapsed following radiation therapy before the sarcoma was diagnosed; these patients were theoretically free of sarcoma at the time of irradiation.

TABLE I. AGE INCIDENCE

AGE (YEARS)	NO. OF PATIENTS
30-39	8
40-49	21
50-59	13
60-69	8
70-79	3
Total	53

Symptoms.—The most common symptoms were abnormal vaginal bleeding, abdominal and back pain, and the presence of an abdominal mass that the patient had palpated (Table II). It is also noteworthy that 4 patients had no complaints, their uterine tumors being discovered during routine medical examination.

TABLE II. PRIMARY AND SECONDARY SYMPTOMS

SYMPTOM	PRIMARY (NO. OF PATIENTS)		SECONDARY (NO. OF PATIENTS)	
Abnormal bleeding		31		4
Menorrhagia	8		0	
Postmenopausal bleeding	10		3	
Irregular bleeding	13		1	
Abdominal pain		5		11
Back pain		2		4
Tumor		3		3
Cough		2		1
Fatigue		2		2
Leukorrhea		1		2
Urinary symptoms		1		2
Diarrhea		1		–
None		4		–

Physical Findings.—A pelvic mass was present in 44 of the 53 cases. Localization in the uterus was evident in 37, with the mass involving the cervix in 7. Ulceration was present in 2 of the latter cases. In the remainder, local extension or recurrence rendered useless any attempts to localize the point of origin.

Other Findings.—Except for hemoglobin determinations which verified clinical pallor in terms of blood-loss anemia, laboratory data did not contribute to the diagnosis.

Thoracic and skeletal roentgenograms revealed pulmonary metastasis on admission in 6 patients. The pulmonary lesions were bilateral in 5. Two patients had metastatic involvement of the spinal column and an additional one had a secondary nodule in a rib.

Pathologic Features

Gross Characteristics.—Pathologic material, all preserved in formalin, included 40 sizable specimens and 13 of biopsy dimensions. Outstanding features of the 40 included an average large size (as compared with benign fibroids), a dark yellowish-tan color, a brainlike consistency, and an irregular or bosselated perimeter with less tendency to separate from the surrounding myometrium than that shown by fibroids. Centrally, there were frequently areas of necrosis, hemorrhage, and cyst formation. Peripherally, large blood vessels were often seen to course over the surface of the tumor when the latter lay near the peritoneum. In 5 tumors there was gross evidence of invasion of the blood vessels (Fig. 1).

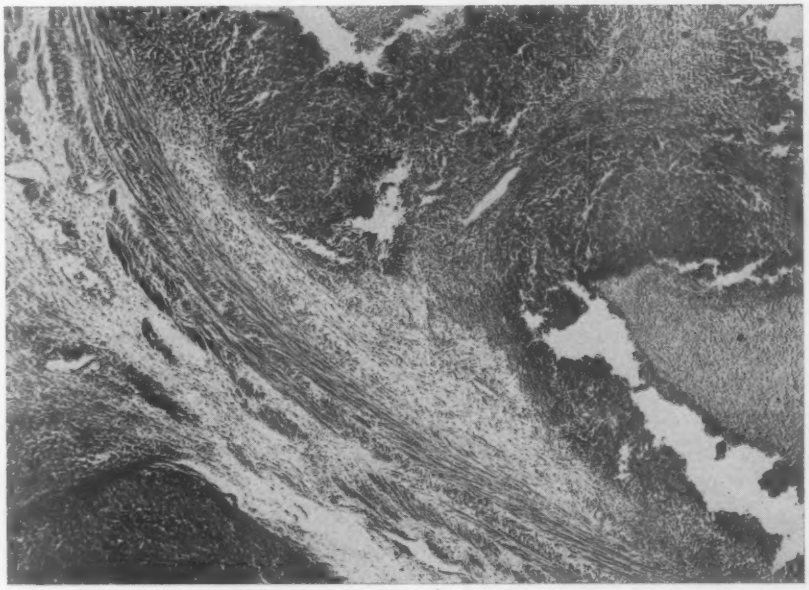

Fig. 1.—Involvement of vein by Grade 4 leiomyosarcoma of uterus. (Hematoxylin and eosin; ×33.)

It was difficult to classify the uterine leiomyosarcomas with respect to site of origin within the uterus. Twenty-five of the 40 gross specimens contained benign myomas (Fig. 2). From the available evidence it was determined that 16 leiomyosarcomas originated within leiomyomas, 12 probably originated in leiomyomas, and 7 originated primarily from the myometrium. For 15 advanced tumors no decision could be reached regarding the site of origin. Three sarcomas were primary in cervical stumps.

Eleven of the 53 tumors appeared to be within the confines of the myometrium, 15 were contained by the serosa but impinged on the endometrium, 5 involved the serosa, and 21 had extended beyond the uterus as determined either by gross inspection or on the basis of clinical and roentgenologic data. In one the extent was unknown.

Microscopic Characteristics.—Spindle cells with elongated nuclei and eosinophilic and finely granular cytoplasm were the basic cellular elements. Cellularity was in general more marked than that observed in leiomyomas, and mitotic figures could always be found. Arrangement in bundles and strands was well demonstrated in the better-differentiated examples, and palisading of nuclei at times recalled the picture of neurofibroma. In the more active growths,

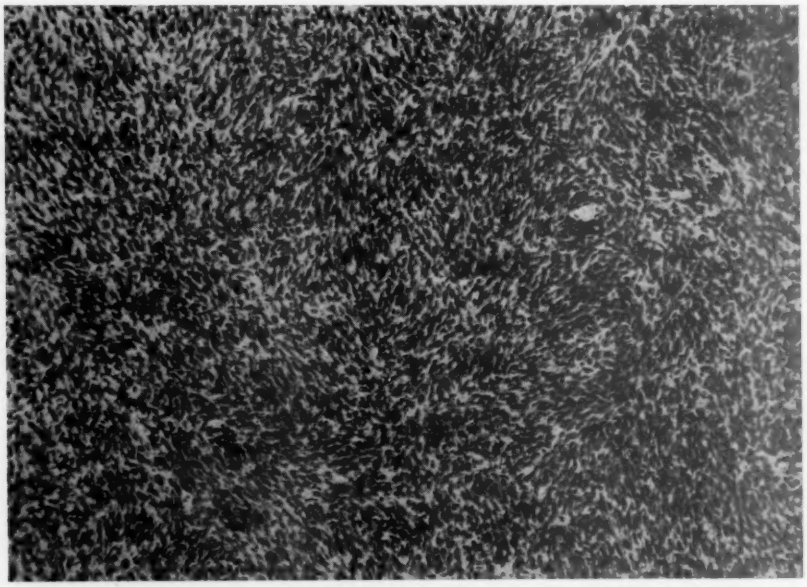

Fig. 2.—Benign cellular myoma. Mitotic activity and pleomorphism were not sufficient for classifying it as a leiomyosarcoma. (Hematoxylin and eosin; ×100.)

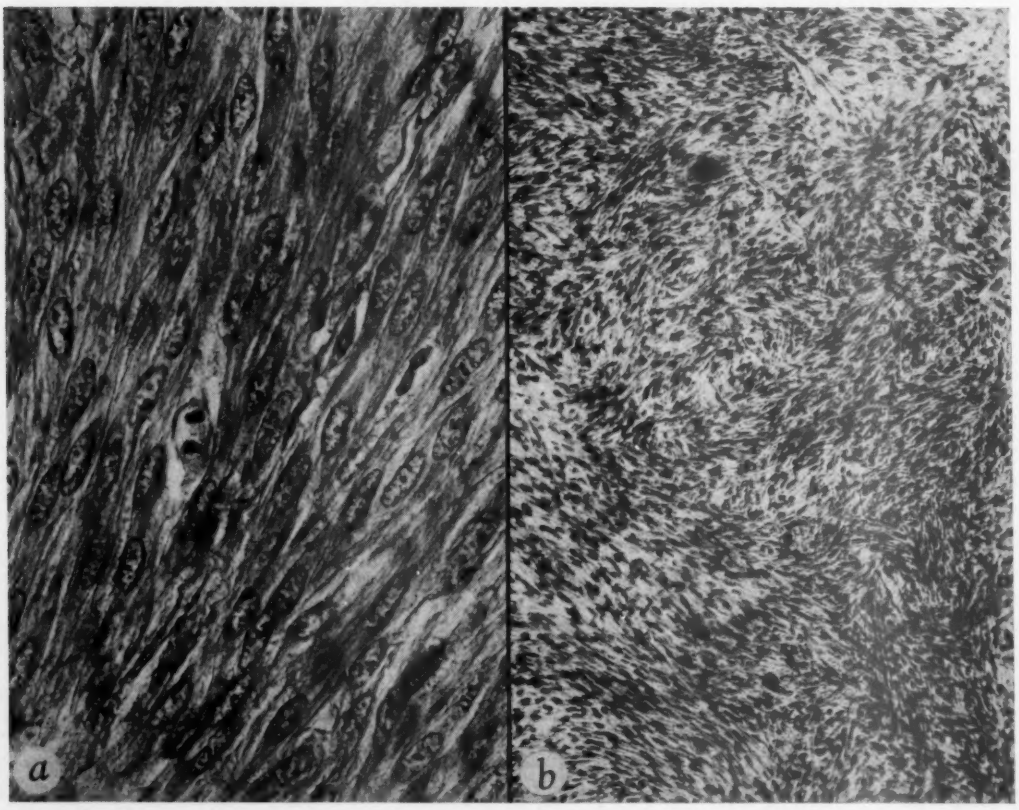

Fig. 3.—Leiomyosarcomas. *a*, Grade 1, showing mitotic figure near center of field. (Hematoxylin and eosin; ×500.) *b*, Grade 2, showing mitotic figures, pleomorphism, cellularity, and a giant cell. (Hematoxylin and eosin; ×100.)

cellular pleomorphism with atypical giant cells often exhibiting atypical mitotic figures was seen. Vascularity was not as pronounced as that observed in stromal endometriosis, and the fibromyxomatous matrix of endometrial sarcoma was lacking in these primary smooth-muscle tumors.

Twenty-one of the 53 tumors contained at least a few giant cells. The presence, absence, or frequency of occurrence of giant cells did not influence the grading of the lesions, or their classification as benign or malignant tumors.

The presence of mitotic activity was considered the most significant factor in deciding that the tumor was malignant, and the degree of such mitotic activity was employed as the principal factor in grading the lesions (Figs. 3 and 4). At a magnification of about 400, a lesion was considered Grade 1 if it contained one mitotic figure per 10 to 20 fields of typical tumor tissue, Grade 2

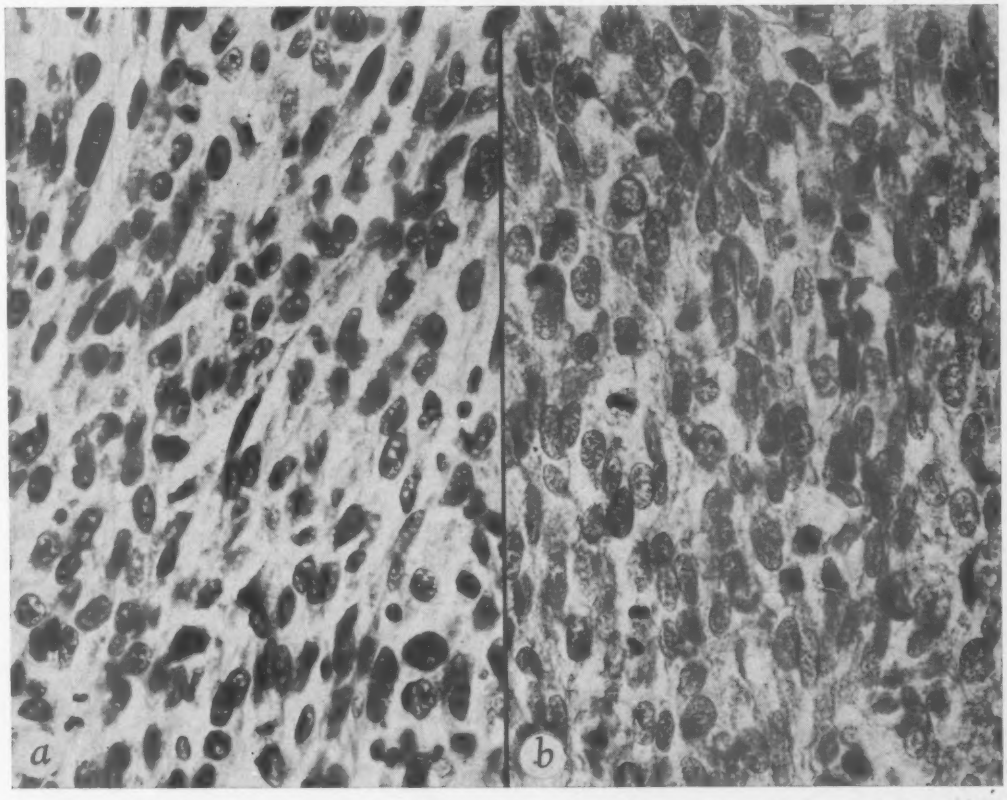

Fig. 4.—Leiomyosarcomas. *a*, Grade 3 showing details of mitotic figures, pleomorphism, cellularity, and loss of polarity. (Hematoxylin and eosin; ×500.) *b*, Grade 4, showing multiple mitotic figures and marked pleomorphism and cellularity. (Hematoxylin and eosin; ×500.)

if it contained one per 2 to 10 fields, Grade 3 if it contained one to 4 per field, and Grade 4 if it contained more than 4 per field. In borderline examples, features of pleomorphism, cellularity, polarity, and cell size were considered secondary in determining the final grade of the lesion.

Originally, there were 72 cases in which a diagnosis of some type of mural sarcoma was made during the 16 year period covered by this study. After careful investigation, 53 cases emerged as cases of leiomyosarcoma of the uterus. The remaining 19 were eliminated for the following reasons: 7 lesions were found on further study to be benign, 6 were of an indeterminate type, 2 were anaplastic carcinomas, one was found to be an endometrial sarcoma, and in 3 the available material was not adequate to confirm the original diagnosis.

Of the 53 leiomyosarcomas, 9 were designated Grade 1, 16 Grade 2, 12 Grade 3, and 16 Grade 4.

In 2 cases regional pelvic lymph nodes were excised at the original operation. As would be expected from what is known of the hematogenous mechanism of metastasis of leiomyosarcoma, these nodes were free of malignant disease.

Treatment

For purposes of relating treatment to end results the patients were divided into 3 groups. Group 1 consisted of 41 patients who received all of their primary definitive treatment at the Mayo Clinic. Group 2 consisted of 5 patients who were primarily treated elsewhere and later obtained modified treatment at our institution. Group 3 consisted of 7 patients who had been primarily treated elsewhere but had such far-advanced sarcomatosis that they received no further therapy at the clinic.

Group 1. Primary Treatment at Clinic.—The treatment of choice at the Mayo Clinic, as illustrated by the 41 patients in this group, was surgical. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on the great majority of these patients (Table III). Five relatively young patients with grossly normal ovaries had total abdominal hysterectomy with unilateral or no oophorectomy.

TABLE III. TREATMENT AND RESULTS IN GROUP PRIMARILY TREATED AT MAYO CLINIC

TREATMENT	NO. OF PATIENTS	LIVING	
		3 YEARS OR MORE	5 YEARS OR MORE
Total abdominal hysterectomy and bilateral salpingo-oophorectomy for cure	21*	14	13
Total abdominal hysterectomy and bilateral salpingo-oophorectomy for palliation only	5†	0	0
Total abdominal hysterectomy and bilateral salpingo-oophorectomy, removal of pelvic nodes	1	0	0
Total abdominal hysterectomy with unilateral or no oophorectomy	5	5	4
Vaginal hysterectomy and bilateral salpingo-oophorectomy	2	2	1
Subtotal hysterectomy	1	0	0
Abdominal removal of tumor only	1‡	0	0
Palliative removal of tumor	1	0	0
Removal of cervical stump, bilateral salpingo-oophorectomy, removal of pelvic nodes	1	1	1
Biopsy and irradiation for palliation	3	0	0
Total	41	22	19

*One lost to follow-up in 1 year.
†One lost to follow-up in 1 month.
‡Lost to follow-up in 2½ years.

Vaginal hysterectomy and bilateral salpingo-oophorectomy were performed in 2 cases. In the first case these operations were chosen because the patient

was very obese and represented a poor surgical risk. In the other case the leiomyosarcoma was an incidental finding following vaginal hysterectomy for uterine prolapse.

Only subtotal hysterectomy and left salpingo-oophorectomy were performed on one patient, as her prognosis was considered hopeless.

A pedunculated leiomyosarcoma was removed abdominally in one case without removal of the uterus or adnexa, because the patient refused hysterectomy. She was living and well 2½ years later, but subsequently has been lost to follow-up.

One patient presented with a primary leiomyosarcoma in a cervical stump. The cervix and both tubes and ovaries as well as the regional pelvic lymph nodes were removed. Three and one-half years later a recurrent lesion in the vaginal vault was removed. The patient remained well until 5 years and 11 months after her original operation, when she had a recurrent lesion in the small intestine. This was removed but 6 months later pulmonary metastasis developed.

Five patients received postoperative roentgen therapy, and 3 received only palliative radium or roentgen therapy.

The 6 patients who were treated with palliative surgical procedures all died within 4 months.

Group 2. Modified Treatment at Clinic.—Five patients received only modified therapy at the Mayo Clinic after receiving their primary surgical treatment elsewhere. Two were given further surgical treatment and 3 were given roentgen therapy. Only one patient in this group lived 5 years or more.

Results of Treatment

Fifty of the 53 patients (94 per cent) have been traced for periods in excess of 5 years following treatment or observation. Of 25 patients with low-grade lesions (Grades 1 and 2), 15 were living 5 years later (Table IV). Of 28 patients with high-grade lesions (Grades 3 and 4), only 5 were living after 5 years.

TABLE IV. RESULTS RELATED TO GRADE OF MALIGNANCY

GRADE OF MALIGNANCY	NO. OF PATIENTS	LIVING	
		3 YEARS OR MORE	5 YEARS OR MORE
Primary Group.—			
1	9	8	8
2	11	7	6
3	9	4	3
4	12	3	2
Total	41	22	19
Modified Group.—			
1	0	0	0
2	2	1	1
3	2	0	0
4	1	0	0
Total	5	1	1
Nontreated Group.—			
1	0	0	0
2	3	0	0
3	1	0	0
4	3	1	0
Total	7	1	0

The relationship between the site of origin of the lesion within the uterus and the results of treatment did not appear to be significant (Table V).

TABLE V. RESULTS RELATED TO ORIGIN OF TUMOR

ORIGIN OF TUMOR	NO. OF PATIENTS	LIVING	
		3 YEARS OR MORE	5 YEARS OR MORE
In leiomyoma	16	7	6
Probably in leiomyoma	12	8	7
Primary in myometrium	7	5	4
Unknown	15	3	2
Cervix	3	1	1
Total	53	24	20

Of 31 patients with lesions apparently limited to the uterus, 18 were living 5 years later (Table VI). Only one of 21 patients who were known to have extension of the tumor beyond the limits of the uterus lived 5 years or more. This patient had a nodular metastatic lesion in the right broad ligament that was removed at the time of total abdominal hysterectomy and bilateral salpingo-oophorectomy.

TABLE VI. RESULTS RELATED TO GROSS ANATOMIC EXTENT OF THE MALIGNANT PROCESS

GROSS EXTENT	NO. OF PATIENTS	LIVING	
		3 YEARS OR MORE	5 YEARS OR MORE
Confined to a leiomyoma	5	3	3
Confined to the myometrium	6	6	5
Extended to endometrium, but not serosa	15	11	9
Extended to serosa, but not endometrium	2	0	0
Extended to serosa and endometrium	3	1	1
Beyond uterus	21	2	1
Unknown	1	1	1
Total	53	24	20

Although 6 patients in this series received postoperative roentgen therapy, it was not possible to evaluate the effects of this therapy as each had received prior surgical treatment.

The 6 patients who received only radiation therapy obtained no apparent benefit from it.

Recurrence or Metastasis.—Recurrence or metastasis of the uterine leiomyosarcoma was known to have developed in 28 of the 53 patients. Some had multiple involvement. Fourteen had metastases to the lungs. Twelve eventually had metastases or recurrence in the pelvic organs, 9 in the abdomen, 5 in the spinal column and five in the vagina.

Comment

The clinical features of the cases in this study were not diagnostic of uterine leiomyosarcoma. Others[3, 17, 21, 25, 30, 32] have made comparable observations.

Although nearly 10 per cent of the patients had prior irradiation when they were theoretically free of malignant disease, it was impossible to establish any definite relationship between the previous irradiation and the production of a uterine sarcoma.

It should be an elementary principle that all patients with pelvic tumors should have a thorough preoperative medical examination, including a roentgenogram of the thorax, to rule out distant metastasis.

Study of the gross pathologic features of the tumors in this series revealed findings similar to those reported by others.[5, 16, 18] Contrary to most reports, it was often impossible to classify the lesions as arising primarily from the myometrium or secondarily in a pre-existing leiomyoma.

Some[4, 14, 15, 27] have demanded evidence of invasion or metastasis before considering a lesion to be a uterine leiomyosarcoma. Only 5 of the leiomyosarcomas in our series were confined entirely within a myoma and therefore failed to present evidence of invasion of the myometrium. In each of these 5 cases, as in all cases in the study, we were convinced by histologic study that the tumors were true leiomyosarcomas. Although 3 of the 5 patients were living 5 years later, one died in 9 months with multiple metastasis. The other was lost to follow-up after one year.

The treatment of choice in leiomyosarcoma of the uterus is total abdominal hysterectomy and bilateral salpingo-oophorectomy. In younger, premenopausal women it might be advisable to conserve ovaries that are grossly normal.

Palliative resection for uterine leiomyosarcoma was apparently of no value and may have been detrimental in some instances. The good results obtained in the 2 patients subjected to vaginal hysterectomy seem to indicate that such treatment, in patients considered to represent poor risks for major abdominal operations, would be far preferable to reliance on radiation therapy.

The apparent failure of radiation therapy in this series supports the many reports[9, 15, 22, 24, 30] that irradiation has been of little or no value in the treatment of leiomyosarcoma of the uterus.

The outlook for patients with low-grade lesions was much better than for those with high-grade lesions. It would thus seem that grading represented a very useful prognostic index for lesions of this type. This has led us to believe that radical resections should be considered, if necessary, not only for the primary therapy of low-grade lesions but also for localized recurrent lesions.

The patients in whom the malignant process had extended beyond the uterus, either to adjacent tissues by direct extension or to distant organs by metastasis, had an almost hopeless outlook. Other authors[1, 8, 19] have pointed out that the extent of the lesion is an important factor in prognosis. This seems to indicate that the prognosis is good only when the leiomyosarcoma is limited to the uterus, where it can be completely removed surgically.

Summary and Conclusions

The clinical and pathologic features of 53 personally studied cases of leiomyosarcoma of the uterus are presented. Of 41 patients who received their primary definitive treatment at the Mayo Clinic, 19 were living at least 5 years after therapy. The clinical features were not diagnostic, but rather suggested other more common pelvic neoplasms. Mitotic activity was considered the most significant factor in determining whether a lesion was

benign or malignant. The treatment of choice was total abdominal hysterectomy. Radiation therapy and palliative surgical treatment were of no apparent value. The grade and extent of the leiomyosarcoma were the most significant prognostic factors.

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Discussion

DR. MALCOLM B. DOCKERTY, Rochester, Minn.—With respect to etiological factors, the observation that these tumors arise only after puberty might suggest an estrogenic influence acting on uterine smooth muscle. It must be recalled, however, that cutaneous, retroperitoneal, and gastrointestinal myomatous tumors affect persons of both sexes and all ages. The history of prior irradiation for benign uterine bleeding elicited from a number of the patients raises another question of etiology. Excellent evidence is available that the development of osteogenic sarcomas and angiosarcomas can be attributed to an irradiation effect. Symmonds and I reported prior use of irradiation in a number of patients who subsequently had sarcoma of the endometrial stroma. Evidence is not so strong for a similar genesis in the case of smooth-muscle tumors.

Still another etiological consideration is possible origin from pre-existing fibromyomas. The older literature gave credence to the notion that the vast majority of uterine myosarcomas began in such benign foci. In the present series it was demonstrated that adequate sampling of the lesion frequently disclosed that the tumors were malignant throughout, despite the fact that encapsulated, low-grade leiomyosarcomas often gave the impression of such a benign origin. Only 16 of the gross specimens contained tumors in which benign and malignant portions occurred side by side.

Every gynecologic surgeon should be familiar with the gross features that enable one to suspect the presence of sarcoma in a myomatous tumor. I am convinced that the problem of recurrence of these neoplasms is compounded by rough manipulation of the tumors, with spillage, during removal, of friable particles of tumor along suture lines and over the peritoneum. Studies of large series of intestinal myosarcomas demonstrate that such seeding is a principal mode of spread. Several vaginal recurrent lesions in the present series almost certainly originated on this basis during vaginal removal of the original tumor. By recognizing this danger during early phases of the operation, the surgeon can isolate the tumor by use of gauze or cellophane. Further protection of peritoneal surfaces and suture lines can be achieved by means of irrigations with saline or mild antiseptics.

Metastasis from leiomyosarcoma practically always is by way of the blood stream. So rarely do these tumors spread by the lymphatic system that operations designed to include removal of regional lymph nodes have practically nothing to recommend them. Gross venous invasion was evident in 5 of the 40 large specimens studied. A relatively large number of the growths metastasized early or late in the lungs and bones. Current work demonstrates that carcinomas and other malignant growths cast showers of tumor emboli into the circulation following surgical manipulation or the simple procedure of biopsy. Thus, it is of more than theoretic value to exercise gentleness in mobilizing these tumors and even to perform preliminary ligation of the large veins leading away from the lesions.

Finally, it is an essential duty of the surgical pathologist to provide his busy colleague in the operating room with immediate data concerning the grade and extent of the lesion removed. Surgical treatment for recurrence of these lesions is rarely successful, and residual tumor tissue almost never responds to irradiation in lesions of this type.

DR. HUBERT L. ALLEN, Alton, Ill.—Most clinicians would agree that the successful treatment of leiomyosarcoma of the uterus is largely a matter of luck; that preoperative diagnosis is not usually made; that this tumor is a highly lethal but unpredictable one; that radiation therapy offers no help; that palliative surgery is of little value; and that the only hope of cure lies in timely hysterectomy. Such an unoptimistic view makes welcome an analysis of a significant number of these cases, as has been presented by Drs. Aaro and Dockerty.

It was thought that the majority of curable sarcomas of the uterus originate in leiomyomas, an idea disputed in this study. We keep this fact in mind when we manage our patients with asymptomatic fibroids. It is apparent that size of the tumor, alone, is not an accurate criterion of sarcomatous change. On the other hand, increase in size and softening of the consistency of uterine tumors have generally been considered to warn of this development, although such histories were not obtained in the cases presented. The occurrence of abnormal uterine bleeding is significant, as is shown by the fact that 31 patients in this series complained of it as a primary symptom. I would like Dr. Aaro to tell us exactly how long we may safely watch our patients with myomas and when we must subject them to hysterectomy. This question usually leads to spirited discussions in staff meetings when cases of leiomyosarcoma are presented.

I think the surgeons at the Mayo Clinic are to be congratulated upon the fact that 19 of the 41 patients whom they treated primarily were alive at least 5 years after treatment. This is a survival rate of 46 per cent and compares very favorably with other reported figures.

I am interested in the matter of immediate pathologic diagnosis of uterine tumors during the course of the operation, which Dr. Aaro says is available to the surgeon because of the routine use of fresh frozen sections for microscopic diagnosis. This would seem to be a lengthy procedure, requiring the study of sections from numerous blocks in order to be effective, and I doubt that many surgeons request such examination while they are performing hysterectomies for myomas. It appears to be a more worthwhile precaution in cases of myomectomy or subtotal removal of the uterus. When total hysterectomy is in progress, the microscopic diagnosis of sarcoma would not alter the procedure significantly.

The authors' conclusion that mitotic activity is the most significant factor in determining the degree of malignancy coincides with the views of many other investigators. This is of prognostic significance, but does not alter treatment, since we believe that postoperative radiotherapy is of little benefit. However, the authors suggest the possible value of resecting local recurrences where the original sections had revealed low-grade mitotic activity. Since 2 patients had had pelvic node dissections with negative findings, it is suggested that this prolonged procedure adds nothing to the survival rate, and this is in line with current ideas of the hematogenous spread of tumor.

No one can dispute the conclusion of the authors that the outlook for the patient improves the more closely the leiomyosarcoma is confined within the uterus. Thus, tumors which are limited to leiomyomas offer the best chance of success in treatment, especially since these usually exhibit the lowest mitosis counts. Conversely, the prognosis worsens the more diffusely the tumor involves the uterus, and is virtually hopeless in cases where tumor cells have spread beyond the uterus either by direct extension or to distant areas by way of the blood stream and lymphatics. It is interesting, however, that there have been some reports of patients with radiologic evidence of tumor spread to lungs or bone who have defied our prognoses and survived for many years—in some cases even showing evidence of spontaneous regression.

AMNIOTIC FLUID EMBOLISM*

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(From the Minnesota Maternal Mortality Committee)

AMNIOTIC fluid embolism is a definite established entity and it is one of the most catastrophic situations encountered in obstetrics. Meyer,[1] in 1926, was the first to describe this disease. Steiner and Lushbaugh's[2] monumental publication in 1941 established this as a definite entity. Prior to that time these deaths were placed in the category of obstetric shock, profound toxemia, idiopathic pulmonary edema, or postpartum hemorrhage. Steiner and Lushbaugh demonstrated particulate matter of the amniotic fluid (meconium, squamous epithelial cells, and vernix caseosa) in the smaller arteries, arterioles, and capillaries of the lungs of these patients. They also reproduced the syndrome experimentally in dogs and rabbits. Subsequent case reports have appeared in the literature substantiating their concept.

It is the purpose of this paper to evaluate some aspects of this entity from data obtained from the Minnesota Maternal Mortality Study. The Minnesota Maternal Mortality Committee made the final decisions with regard to each case after an obstetrician-investigator obtained complete data by reviewing the hospital medical records and prenatal records and interviewing the various personnel involved. Details of the organization of this committee and the mechanics of the study have been published.[3, 4] All slides regarding microscopic examination of the lungs of these patients were reviewed by us. In one instance where the microscopic diagnosis was in doubt, this was confirmed by Steiner.[5] It is our impression that a series of 15 cases of this rare entity is worthy of presentation since the largest previously reported series was Steiner and Lushbaugh's[2] 8 cases.

Incidence

The disease is quite rare. During the first 7 years of the Minnesota Maternal Mortality Study[6] there were 370 maternal deaths among 559,843 live births. The committee classified 234 of these deaths as obstetrical (Table I) and 136 as nonobstetrical (medical, surgical, homicides, accidents, etc.). Amniotic fluid embolism was ranked as the fifth category with regard to frequency as a cause of obstetrical deaths. There were 15 deaths from amniotic fluid embolism among 559,843 live births, an incidence of 1 per 37,323 live births. There are undoubtedly sublethal cases as reported in the literature but these are always questioned since the true diagnosis is made only at autopsy.

*Presented at the Twenty-sixth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., Oct. 2-4, 1958.

Predisposing Factors

Steiner and Lushbaugh showed the predisposing factors to be uterine tetany or exceptionally strong uterine contractions, meconium in the amniotic fluid, intrauterine death, an oversized baby, advancing age of the mother, and multiparity. The 15 cases from the Minnesota Maternal Mortality Study provide a large series of this rare entity for analysis even though this number has limitations as far as statistical evaluation is concerned. Of the 15 cases, the diagnosis was established by autopsy in 12 and by aspiration of blood from the right heart immediately post mortem, according to the method described by Gross and Benz[7] in 1. In the other 2 cases, autopsy was refused but the clinical picture was so typical that the committee included these as probably amniotic fluid embolism deaths. Both of these patients had normal findings prior to uncomplicated deliveries, then suddenly developed restlessness, dyspnea, cyanosis, and profound shock. Steiner and Lushbaugh are of the opinion that the clinical diagnosis is possible before death if the above findings are present.

TABLE I. OBSTETRICAL CAUSES OF DEATH

CAUSE OF DEATH		NO.	%
Hemorrhage		65	27.8
Toxemia		46	19.7
Infection		35	15.0
Heart disease		19	8.1
Amniotic fluid embolism		15	6.4
Anesthesia		10	4.3
Chorionepithelioma		9	3.8
Air embolism		6	2.6
Others		29	12.4
Not determinable	9		
Transfusion deaths	4		
Dehydration and electrolyte imbalance	4		
Idiopathic pulmonary edema	4		
Suicide (postpartum psychosis)	3		
Pituitrin shock	2		
Diabetes mellitus	2		
Unexplained shock	1		
Total		234	100.1

TABLE II. TYPE OF UTERINE CONTRACTIONS

TYPE	NO.
Hard (every 1 to 2 min.)	8
Hard (tetanic)	6
None (cesarean section)	1
Total	15

Tables II and III support Steiner and Lushbaugh's findings. They postulated that excessively powerful contractions prepared a route for the entrance of the emboli into the maternal uterine sinuses by loosening or tearing the placenta and membranes and then forced the emboli into these channels. In a perusal of the literature the one common denominator in this disease seems to be tumultuous labor or exceptionally strong uterine contractions. Table II analyzes the type of uterine contractions. One patient had no labor and the disease occurred during elective cesarean section. It seems significant that of the 14 patients with tetanic or exceptionally strong contractions, 7 (50 per cent) had pituitary extract during labor. Four of these had induction of labor (2 by Pituitrin subcutaneously and 2 by intravenous Pitocin drip) and in only one instance was the induction considered indicated by the committee. In the other 3, pituitary extract subcutaneously was used injudiciously

during normal labor. It seems safe to state that in these 7 patients the use of pituitary extract contributed to the production of amniotic fluid embolism through the medium of vigorous labor. The careless use of this drug, therefore, must be implicated in the etiology of this disease. The following 2 case protocols of pituitary extract stimulation are illustrative of this group of 7.

TABLE III. PARITY

PARITY	NO.
i	2
ii	4
iii	5
iv	2
v	1
vi	1
Total	15

CASE 1.—This patient was a 24-year-old para i who had a completely uneventful antenatal course. She was admitted to the hospital for elective induction of labor because she was 3 weeks overdue by history. The vertex was floating and the cervix was "hard" and barely admitted one finger. An attempt to rupture the membranes was unsuccessful. Intravenous Pitocin infusion (6 minims in 500 c.c. of fluid) was given over a period of 3 hours and 15 minutes in the morning. Contractions occurred every 2 to 3 minutes and lasted 30 seconds but ceased with the termination of the infusion. There was no progress in cervical dilatation or effacement. Repeat Pitocin infusion of the same concentration was given in the afternoon of the first hospital day but no active labor developed. Sterile vaginal examination in the evening revealed the status of the cervix to be the same and another attempt to rupture the membranes failed. A third bottle of Pitocin infusion of the same concentration was given between 7 P.M. and midnight but no active labor developed.

At 1 A.M. of the second hospital day the patient developed a chill and fever of 102° F. Blood culture was obtained and was subsequently reported as sterile. Physical examination was normal and fetal heart tones were normal. Treatment consisted of large doses of penicillin and Achromycin. At 8 A.M. the membranes were ruptured artificially. At 9 A.M. the fourth bottle of Pitocin infusion (same concentration) was started and this was completed at 2 P.M. No active labor developed. Her temperature at 5 P.M. was 102° F. but she looked and felt well. X-rays showed the vertex floating in left occipitotransverse to left occipitoposterior position.

In the morning of the third hospital day the temperature was normal. The fifth bottle of Pitocin infusion (same concentration) was started at 10:45 A.M. at 16 drops per minute but was increased by the nurses to 48 drops per minute by noon. The uterus was described by the nurses as "hard almost constantly" but no progress in dilatation of the cervix was evident. At 3 P.M. the fetal heart tones were 176 and the blood pressure was normal. At 3:40 P.M. she began to make good progress. The hard, almost continuous contractions continued. The nurses decreased the infusion to 10 drops per minute and Demerol, 75 mg., with scopolamine, 1/200 grain, was given. By 3:55 P.M. the cervix was 6 cm. dilated and by 4 P.M. the cervix was completely dilated with the vertex at plus 2 station. The Pitocin infusion was discontinued and as the patient was being moved to the delivery room, she suddenly became cyanotic, gasped for air, and developed a generalized convulsion. A tongue blade was inserted and oxygen administered. No pulse or blood pressure could be obtained and no fetal heart tones could be heard. Adrenalin, 1 c.c., was given intravenously and cardiac massage was carried out without success. Postmortem cesarean section was done with the delivery of a stillborn infant weighing 3,390 grams.

At autopsy the right auricle seemed somewhat dilated. The blood in the right auricle was liquid and failed to clot during the next 24 hours. During this time particles up to 2 mm. in size and small hair floated to the surface. Complete autopsy was otherwise negative except for the typical picture of amniotic fluid embolism on microscopic examination of the lungs (Fig. 1).

CASE 2.—This patient was a 26-year-old para ii who also had a completely uneventful antenatal course. She was admitted to the hospital on the estimated date of confinement for elective induction because she was "apprehensive and to get it over with." She was given castor oil, enema, and Upsher-Smith powdered ergot orally, 6 grains, at 8:30 A.M., 9:00 A.M., and 9:30 A.M. without labor resulting. Obstetrical Pituitrin, 3 minims, subcutaneously, was given every 20 minutes for 5 doses beginning at 10:20 A.M. By noon uterine contractions had begun. The membranes were ruptured artificially at 2:30 P.M. The cervix barely admitted a finger and the fetus was presenting by the vertex. Contractions were occurring every 5 to

Fig. 1.

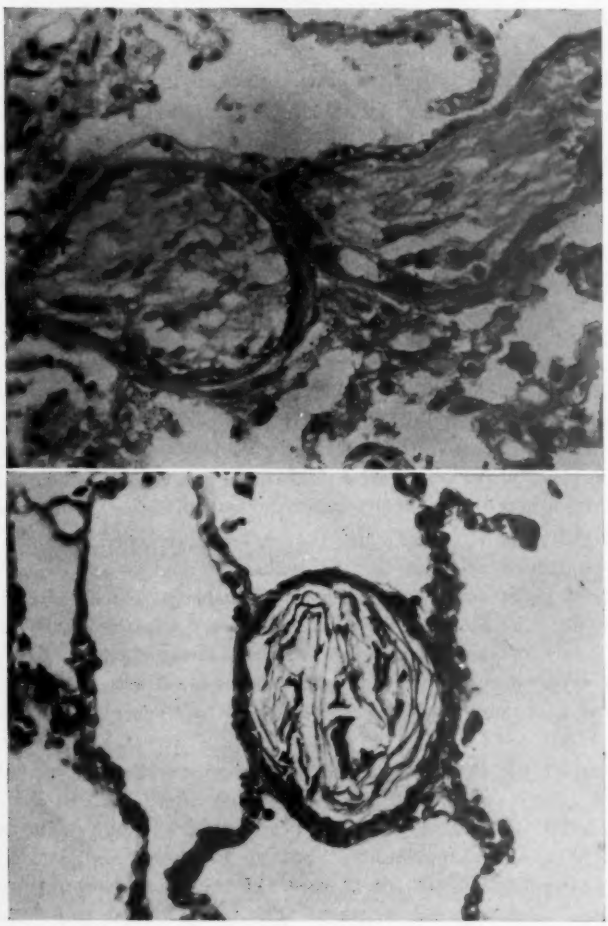

Fig. 2.

Fig. 1.—Dilated pulmonary arterioles containing mucin (meconium) with leukocytes and an occasional degenerated epithelial cell as an embolus. (×390; reduced ¼.)

Fig. 2.—Dilated pulmonary arteriole containing a mass of mucin (meconium) and epithelial squamae as an embolus. (×390; reduced ¼.)

10 minutes and obstetrical Pituitrin, 3 minims subcutaneously, was given every 20 minutes for 3 doses beginning at 3:15 P.M. By 4 P.M. the patient was having hard contractions every 1 to 2 minutes lasting 45 seconds to one minute. At 5:15 P.M. the face was flushed. At 5:30 P.M. she was having chills and perspiring and became dyspneic and apprehensive. No radial pulse could be felt and the blood pressure was 70/40. Coramine, 5 c.c., was given intramuscularly. Fetal heart tones were normal; the cervix admitted one finger and there was no abdominal tenderness. The fingernails and abdomen appeared cyanotic. During the next 45 minutes her condition returned to "normal." Demerol, 100 mg., with scopolamine, 1/150 grain, was given at 6:30 P.M.

By 8 P.M. the cervix was 5 to 6 cm. dilated and at 8:30 P.M. she was moved to the delivery room and was given nitrous oxide and oxygen with contractions, which were hard and occurring as previously noted. Cyclopropane anesthesia was started at 8:55 P.M. and outlet forceps extraction of a living female infant weighing 7 pounds, 3 ounces, was carried out at 8:56 P.M. Anesthesia was discontinued at 9 P.M. and the placenta was expressed at 9:05 P.M. The pulse rate was recorded as 108 and respirations at 22. As the patient was being transferred to her room at 9:20 P.M., she suddenly became restless, dyspneic, cyanotic, and pulseless. The blood pressure was 80/48. In spite of treatment with oxygen, Coramine, whole blood, and Levophed, the patient died 2 hours and 40 minutes later. Autopsy was negative except for typical amniotic fluid embolism (Fig. 2).

Several authors[8-11] have alluded to pituitary extract as an etiological factor in the production of tumultuous labor.

Parity (excluding the present pregnancy) is shown in Table III. It is interesting to note that there were no primigravidas in this series. Age distribution (Table IV) shows that this entity can occur at any age during the reproductive period.

TABLE IV. AGE OF PATIENTS

AGE (YEARS)	NO.
20-24	2
25-29	3
30-34	7
35-39	3
Total	15

Table V presents the stage of gestation at the time of death. Almost one half of these patients were past the calculated date of confinement.

TABLE V. WEEKS OF GESTATION

WEEKS	NO.
38	2
39	2
40	4
41	2
42	2
43	3
Total	15

Infant weight at birth is given in Table VI. There was not a single excessive-sized infant in contradistinction to Steiner and Lushbaugh's report of 4 in 8 cases.

TABLE VI. WEIGHTS OF INFANTS

WEIGHT (POUNDS)	NO.
Undelivered	4
5-5½	3
6-6½	4
7-7½	4
8	1
Total	16*

*Includes one set of twins.

The outcome of the fetus is shown in Table VII. In Steiner and Lushbaugh's 8 cases, there were 4 intrauterine deaths before the onset of labor. This was not so in a single instance in our series.

TABLE VII. CONDITION OF FETUS

CONDITION	NO.
Undelivered (viable until death of mother)	4
Living and well	10
Stillborn (viable until shock in mother)	1
Died 3 hours post delivery	1
Total	16*

*Includes one set of twins.

The amniotic fluid was described as meconium-stained in 4, not described in 10, and clear in one (at cesarean section). In Steiner and Lushbaugh's 8 patients, 4 had meconium-stained amniotic fluid.

A review of the literature shows the membranes had ruptured (spontaneously or artificially) prior to the onset of the symptoms in the majority of cases. The results of the Minnesota series are in accordance with these findings. The membranes had ruptured prior to the onset of symptoms in 14 (8 spontaneously and 6 artificially including one at the time of cesarean section). One patient died at complete dilatation of the cervix with the membranes bulging at the introitus. Steiner and Lushbaugh did not comment regarding rupture of the membranes as a predisposing factor. In their 8 protocols, membrane rupture was mentioned in only one case.

Mode of Entrance of Amniotic Fluid Into Maternal Circulation

The mode of entrance of the amniotic fluid into the maternal circulation is unknown. The postulation with regard to tumultuous labor has been discussed above. Following rupture of the membranes it is conceivable that the amniotic fluid may dissect between the membranes and the uterine wall and enter the venous sinusoids. In cases of rupture of the uterus, cesarean section, premature separation of the placenta, and placenta previa, the amniotic fluid has easy access directly into the maternal circulation. In Steiner and Lushbaugh's series of 8 cases, one showed a ruptured uterus at autopsy. In the Minnesota series, 2 of the 15 patients had ruptures of the lower uterine segment. This in itself is usually enough to cause death, but after careful evaluation the committee assessed amniotic fluid embolism which was demonstrated unequivocally at autopsy as the primary cause of death. One patient died within 28 minutes after the beginning of symptoms and the estimated blood loss was 700 to 1,000 c.c. The other died within 1 hour and 20 minutes and the rupture of the uterus followed administration of intravenous Pitocin solution for induction of labor. There was absence of massive hemorrhage and the patient was given 200 c.c. of plasma and 500 c.c. of whole blood. Shotton and Taylor[12] and Reid and associates[10] are of the opinion that the more frequent outlet for the fluid is through the endocervical veins.

Incidence of Defects in Blood Coagulation

Steiner and Lushbaugh recorded 4 of their 8 patients as having postpartum hemorrhage (1,500 c.c., 1,000 c.c., 1,000 c.c., and 500 c.c.). No mention was made of incoagulability of the blood. They postulated that the uterine atony might be secondary to shock or possibly to a relaxation of smooth muscle as part of the anaphylactoid reaction. Hemmings,[13] Dooley and Leary,[14] and Eames[15] were the first to make observations which established that, during life, the circulating blood may become incoagulable as a result of amniotic fluid embolism. Ratnoff and Vosburgh[16] presented the first case of documented afibrinogenemia with amniotic fluid embolism. Weiner and

co-workers[17] were the first to demonstrate that amniotic fluid contains a thromboplastin-like substance. It has been established that the placenta and decidua are rich in thromboplastin.

It is clear that some patients with amniotic fluid embolism develop incoagulability of the blood but the mechanism of this remains unknown. The pathogenesis is similar, if not the same, as in certain cases of abruptio placentae and intrauterine death. In these situations it is the hypothesis that thromboplastin is released into the maternal circulation and results in intravascular clotting and defibrination of the blood. This concept is largely the result of the works of Reid, Weiner, Ratnoff, Schneider, and others. These patients may also present decrease in platelets, prothrombin, and accelerator factors with increase in fibrinolysins. Schneider[18] believed that the clotting defect in amniotic fluid embolism is due to a heparin-like material in the circulating blood.

The clinical diagnosis becomes obvious when it is observed during the bleeding emergencies that the blood does not clot. If laboratory facilities are available, a plasma fibrinogen determination should be done. Normal values are 200 to 600 mg. per cent. A fibrinogen level less than 150 mg. per cent is abnormal. The clot observation test is a rapid and practical method of diagnosis. Five cubic centimeters of the patient's blood is placed in a clean test tube. Normal blood will clot within 8 to 12 minutes and the clot remains intact for at least 24 hours. In afibrinogenemia or hypofibrinogenemia the blood may not clot at all, or, if it does so, may undergo partial or complete dissolution within 30 to 60 minutes.

In the Minnesota series of 15 cases of amniotic fluid embolism, 4 manifested incoagulability of the blood. In one patient the only notation made was that the blood was not clotting. In the other 3, in addition to this observation, clot observation tests were carried out and no clotting was observed. One patient died before blood replacement could be started, the second received 865 c.c. of whole blood, the third 4,350 c.c., and the fourth 2,000 c.c. before death occurred. The fourth patient, after the first 500 c.c. of blood, was given 3.17 Gm. of fibrinogen and the plasma fibrinogen level was then determined at 200 mg. per cent. Two of these 4 patients also demonstrated bleeding other than postpartum hemorrhage. One showed bleeding from all venepuncture sites and developed ecchymoses over the vulva and perineum. The other showed, at autopsy, unclotted blood in the right broad ligament and right gutter (no evidence of ruptured uterus) and unclotted blood in the stomach and small bowel.

Mechanism of Maternal Death

The cause of the patient's death remains another unknown aspect of the disease. The symptomatology of the process seems fairly uniform throughout the cases in the literature. The patient may have a chill or feel cold; then she becomes restless or apprehensive, dyspneic, and cyanotic, and profound shock appears. Unlike venous thrombotic embolism, pain in the chest is a rare complaint. This is corroborated by the Minnesota Maternal Mortality series. Of the 15 patients, only one complained of chest pain. Pulmonary edema may be present. In cases where the embolism is massive to the pulmonary vascular tree, there is mechanical blockage with subsequent acute pulmonary hypertension (cor pulmonale) and acute dilatation of the right heart. Steiner and Lushbaugh are of the opinion that the mechanism is predominantly one of anaphylactoid shock combined with the mechanical blockage. They suggest that death might be due to nervous reflexes initiated in the lung by the emboli causing cardiac depression and pulmonary vascular

spasm. Reflex bronchospasm is probably also present. In cases complicated by hypofibrinogenemia or afibrinogenemia, hemorrhagic shock is an added insult.

Other Clinical Data From the Minnesota Series

All 15 patients were perfectly well before this final illness except 2 who were obese, 1 with essential hypertension, and 1 with mild pre-eclampsia. Regarding fetal presentation, 13 were vertex, 2 breech, and one mentum anterior (one set of twins). With reference to the type of delivery, 4 patients died undelivered during labor, 4 were delivered spontaneously, 5 by outlet forceps, one by breech extraction, and one by elective cesarean section. Of the 14 patients who experienced labor, the 4 who died undelivered had labors varying from 3½ hours to 7 hours, and of the 10 who were delivered, the length of labor varied from 1½ hours to 22 hours. There were no anesthesia complications. In fact, 5 patients had no anesthesia; 7 received various inhalation gases as analgesia with contractions; and only 3 were anesthetized (cyclopropane, Pentothal and curare, and ether with nitrous oxide and oxygen). The rapidity with which death occurred is illustrated by Table VIII.

TABLE VIII. TIME BETWEEN ONSET OF SYMPTOMS AND DEATH

TIME	NO.
Less than 30 minutes	5
1 to 2 hours	4
4 to 5 hours	3
6 hours	2
9 hours	1
Total	15

Treatment of Amniotic Fluid Embolism

Although a few presumptive sublethal cases of amniotic fluid embolism with recovery have been reported in the literature, the disease is almost always fatal. To establish an undisputable diagnosis it is necessary to demonstrate amniotic particulate matter in the pulmonary vessels and this is not possible except at autopsy. The entity is so infrequent that the physician is not constantly alert to its possibility. Rapid action is necessary if there is to be any possibility of saving the patient. Oxygen therapy is indicated. Morphine is the best drug for the restlessness and apprehension and should be given even in the presence of cyanosis and shock. Intravenous injections of papaverine and atropine are indicated to block off vagal effects and relieve spasm of the blood vessels and bronchial tree. Aminophylline may also be used in this regard. Epinephrine is probably contraindicated because of its constrictive effect on arterioles already partially constricted. The withholding of intravenous fluids and blood in the presence of acute pulmonary edema is very important. Tourniquets to the limbs or phlebotomy might be efficacious in the presence of acute pulmonary edema.

In cases of incoagulability of the blood, fibrinogen and fresh whole blood are indicated. According to Reid and associates,[10] the amount of fibrinogen required should be equivalent to that contained in the circulating blood (8 to 12 Gm.) because, theoretically, complete defibrination is possible. A minimum of 4 Gm. is necessary, but possibly 3 times that amount might be required before normal clotting and hemostasis are restored. As an aid in the diagnosis of sublethal cases, it has occurred to us that it might be useful to perform cardiac catheterization to obtain blood from the right heart. This could then be examined according to the method of Gross and Benz.[7]

Summary and Conclusions

1. An analysis of 15 cases of amniotic fluid embolism from the Minnesota Maternal Mortality Study with a discussion of some of the clinical, physiological, and pathological aspects of this disease has been presented. The incidence was one per 37,323 live births.

2. The commonest of predisposing factors was the tumultuous labor or exceptionally strong uterine contractions noted in 14 of the 15 patients. One patient had no labor because she was delivered by elective cesarean section.

3. Of these 14 patients, 7 (50 per cent) had had pituitary extract during labor. It seems safe to state that in these 7 patients, the use of pituitary extract contributed to the production of amniotic fluid embolism.

4. The membranes had ruptured prior to the onset of the symptoms in 14 of the 15 patients (8 spontaneously and 6 artificially including one at the time of cesarean section).

5. Four of the 15 patients manifested incoagulability of the blood.

6. The warning of Eastman[19] is well taken and is still applicable today. He warns us not to make this a wastebasket for all cases of unexplained death in labor.

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4959 EXCELSIOR BLVD.

Discussion

DR. HERMAN I. KANTOR, Dallas, Texas.—The report of 15 patients with amniotic fluid embolism is a landmark in the study of a disease still considered a rare obstetric complication. As late as 1951, a 10 year maternal mortality study from Charity Hospital in New Orleans listed no deaths from this disease. It is surprising and perhaps shocking to see that, in this Minnesota Maternal Mortality Study, it is ahead of deaths from anesthesia, 15 to 10. I doubt if the cold environs of Minnesota are more conducive to such embolization than the sunny warmth of New Orleans. As a matter of fact, the syndrome was first identified in Brazil by Meyer.

Within recent years in the Dallas Hospitals we have had 2 patients in whom death from amniotic fluid embolism was proved by autopsy. Finding particulate elements characteristic of amniotic fluid in the maternal pulmonary vessels is pathognomonic. Studies indicate that it is never physiologic for even small quantities of amniotic fluid to enter the maternal circulation. When the typical syndrome described by the authors makes a dramatic appearance, amniotic fluid embolism must be suspected.

In one of our 2 patients, induction with Pitocin was attempted unsuccessfully. Labor started spontaneously 2 days later. When explanations of this strange phenomenon are sought, it becomes easy to indict Pituitrin if it has been given. Hard labor is often difficult to evaluate clinically. The judicious use of Pituitrin must not be condemned on this basis, although its injudicious use must be berated.

The association of clotting defects with amniotic fluid embolism creates an intricate change in normal physiology. Afibrinogenemia was present in the second of our patients. Since, among the patients reported in the literature it occurs in about 40 per cent, it may serve as an important diagnostic sign in patients who survive this complication. However, it is indistinguishable from the afibrinogenemia which may occur in placental separation or intrauterine fetal death.

There appear to be at least 3 mechanisms by which the afibrinogenemia may develop (Fig. 1).

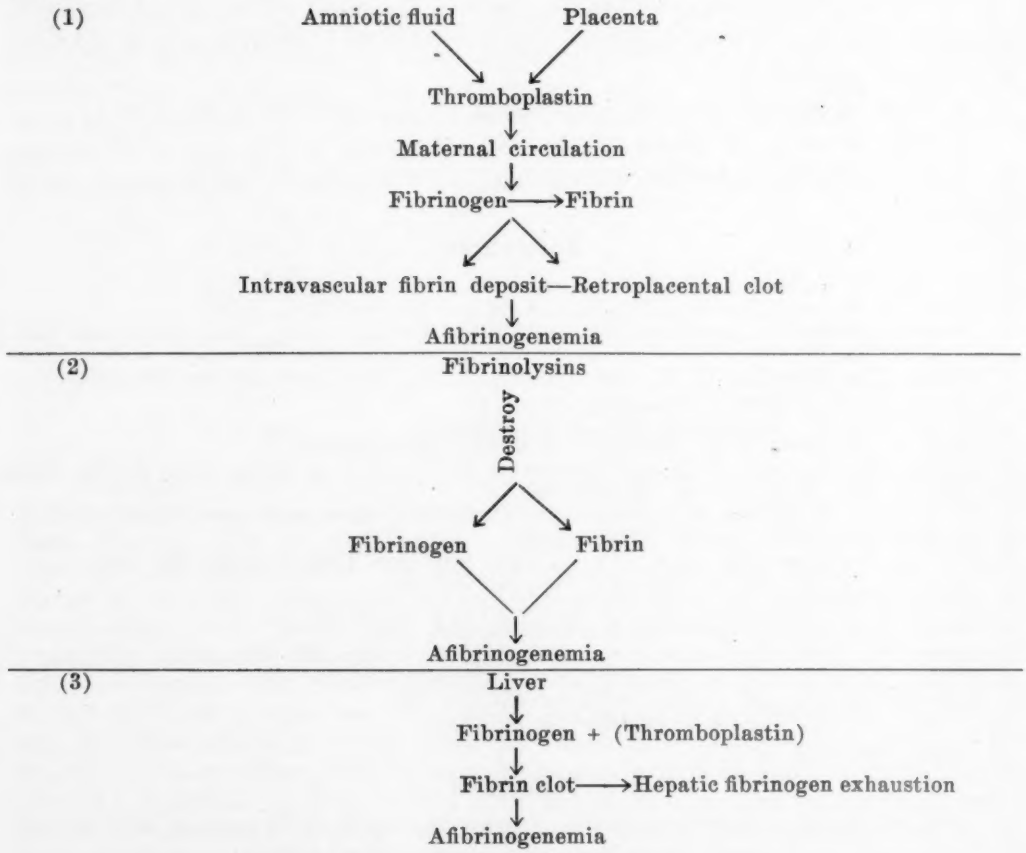

Fig. 1.—Suggested mechanisms—afibrinogenemia.

1. Amniotic fluid and placental tissue have been shown to possess thromboplastic activity. When this thromboplastic substance enters the maternal circulation, fibrinogen is converted to fibrin and deposited intravascularly. These may be demonstrated in tissue studies. Also, much fibrinogen may be lost in forming a retroplacental clot.

2. The liberation of fibrinolysins, which have sometimes been demonstrated, further complicates the situation. They destroy fibrinogen as well as fibrin, and thus decrease fibrinogen levels further.

3. Fibrinogen is normally replaced by the liver. When it is lost at a rapid rate, hepatic exhaustion may follow, and the normal fibrinogen blood level cannot be maintained.

Probably the mother can tolerate small amounts of amniotic fluid in her circulation without symptoms. Experimentally in one patient, 8 c.c. was injected intravenously without demonstrable effect. To understand the phenomenon fully, it seems plausible to postulate a situation in which fairly large amounts are infused directly into the maternal veins.

The following may be a possible mechanism to explain amniotic fluid infusion: the small placental separation opens maternal sinuses; the break in the fetal membranes at this point causes the contracting uterus to act as an efficient pumping mechanism. (Fig. 2).

In the authors' presentation, one patient sustained embolism during cesarean section. The explanation must be that direct infusion occurred at the time of the uterine incision. Moreover, it might be possible to correlate the time of embolism with the administration of an oxytocic.

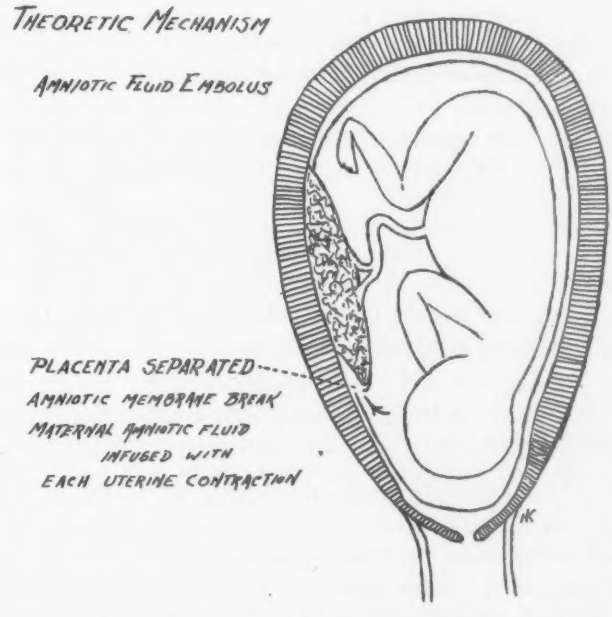

Fig. 2.—Possible pathogenesis, amniotic fluid embolism.

In conclusion I should like to ask two questions:

1. Were any studies made to demonstrate clotting defects in the newborn?

2. The relationship of Pituitrin to obstetric complications is often investigated. What is the incidence of Pituitrin induction of labor for the total number of deliveries in this 7 year study?

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DR. ANTHONY RUPPERSBERG, JR., Columbus, Ohio.—I should like to add twelve cases to Dr. Barno's series from 2 of our Maternal Mortality Studies, established in Ohio.

1. The Franklin County Maternal Mortality Study has just completed its tenth consecutive year of operation by the Columbus Obstetric-Gynecologic Society. There were 2 cases of amniotic fluid embolism in 180 cases compiled in 10 years (1948 to 1957). One

case is included in the Ohio Maternal Mortality Study. Neither patient had had Pitocin administered; both died undelivered and were dead on arrival at the hospitals. One patient, aged 38, entered labor at term spontaneously, with a central placenta previa located over a cervix which was obliterated by some previous surgical procedure. The other, aged 32, near term, developed convulsions at home and was dead on arrival at the hospital. The diagnosis was proved by autopsy in both cases.

2. The Ohio Maternal Mortality Study covers 88 counties of the state and has been operated since 1955 by the Ohio State Medical Association. To date, 408 cases have been collected and 11 cases of amniotic fluid embolism are reported at this time. In 3 of the cases afibrinogenemia was also entered as a cause of death. All cases were studied at autopsy.

The use of Pitocin was not recorded in the history of any case. Active tumultuous labor occurred in only 3 patients, after rupture of the amnion. All 3 were at term, 2 were delivered spontaneously, and one died undelivered. An immediate postmortem cesarean section delivered a living infant from the latter patient.

One patient had a pregnancy of 11 weeks' gestation; the remaining 10 had pregnancies of 36 weeks or more.

In the 11 patients with amniotic fluid embolism, 6 died undelivered. Four fetuses were dead, but 2 patients were delivered of living infants, one of whom bore a set of twins. The twins died shortly after birth.

Abruptio placentae was recorded in only one case of the 11. Convulsions, frequently appearing as a terminal sign, were often diagnosed as "eclamptic seizures" by the astonished observer.

Although the cases we studied in Ohio reveal no relationship to Pitocin as an etiological factor in producing this catastrophic condition, we should continue to use the drug cautiously.

DR. BARNO (Closing).—I wish to thank Drs. Kantor and Ruppersberg for their remarks. Dr. Kantor asks two questions. In answer to the first question, the Minnesota Maternal Mortality Study is confined to maternal deaths only and no studies of the newborn were carried out. Regarding the second question, we are in the process at the present time of analyzing the total problem of pituitary extract in labor and the results will be published in the near future. We have analyzed the deaths due to hemorrhage and have found that 50 per cent of these were caused by ruptured uteri and/or lacerations of the cervix. Two-thirds of the ruptured uteri and/or lacerations of the cervix were due to the injudicious use of pituitary extract and accouchement forcé—equally divided in each category. Thus, the problem of injudicious use of pituitary extract continues to be a problem in present-day obstetrics.

MANAGEMENT OF MISSED ABORTION IN PRIVATE PRACTICE*

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RETENTION of the products of conception in missed abortion is not only a tragedy to the patient but also a waste of valuable time taken from the all too short reproductive years of her life. The false notion that toxins are absorbed from the degenerated retained pregnancy has long since been laid to rest but the psychological trauma to the patient of "carrying a dead baby" is a very real thing. Opposed to this is the possibility of trauma and morbidity attendant upon surgical evacuation of the uterus.

Since the incidence of this condition is so low and because so little attention has been paid to it, no one individual can see or collect enough cases to reach conclusions of statistical significance. Thus, trends, impressions, and personal opinions are expressed dogmatically. For the private practitioner, who sees only a few such cases in a professional lifetime, there is no clear-cut guide for management of these unfortunate patients. Instead, of the few opinions recorded, there is about equal division into completely opposite methods of treatment.

Traditionally the therapy of missed abortion is conservative. Reassurance of the patient while awaiting spontaneous evacuation of the degenerated products of conception is the rule. That this problem is far from settled is shown by a recent return to surgical evacuation of the uterus, either by curettage or hysterotomy, because of the fear of possible severe hemorrhage, the development of afibrinogenemia, or infection.

Textbooks differ widely in suggested therapy. Eastman[1] advocates unqualified noninterference, while Greenhill[2] advises evacuation of the uterus by curettage or vaginal hysterotomy if the contents are not expelled spontaneously within 4 weeks of the time of definite diagnosis. Kimbrough[3] states that, in the first trimester, evacuation of the uterus should be carried out as soon as the diagnosis is certain, while in the second trimester spontaneous evacuation should be awaited unless constitutional symptoms demand interference, and that dilute intravenous posterior pituitary extract should be used for several days prior to operative intervention. Beck[4] advises large doses of estrogen followed by posterior pituitary extract and, if this is unsuccessful, the uterus should be emptied by the procedure best suited to the conditions present.

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A review of the recent obstetrical literature shows only two papers on the subject and a few scattered case reports on the development of afibrinogenemia associated with missed abortion. It is not surprising to find that these two reports are diametrically opposed as to methods of treatment, but both authors acknowledge that they have too few cases from which to draw valid conclusions.

Fisher[5] collected 30 cases of missed abortion from 4 Baltimore hospitals over a 20 year period. There was no medical indication for termination in any of these cases. He found that of 19 patients whose uteri were evacuated surgically 3 were morbid postoperatively, while the remaining 9 women, in whom the condition was allowed to terminate spontaneously, had no complications. Naturally, he advised conservative management.

In contradistinction to this, Bivens[6] treated 12 of 23 patients surgically with only one complication, a 400 to 500 c.c. hemorrhage. Eleven patients were allowed to abort spontaneously with curettage used for completion of the abortion 3 times and with severe hemorrhage in 3 patients. Based on these results, he advocates surgical termination by dilatation and curettage when the uterus is smaller than the size of a 3 months' gestation. In larger uteri, artificial rupture of the membranes and induction of labor with dilute intravenous posterior pituitary extract with antibiotic coverage should be used. Hysterotomy either vaginally or abdominally is suggested for the few that do not respond to 2 or 3 inductions.

Material

Ten women with 11 missed abortions were cared for by the author during a 3 year period ending December, 1957. One patient had two such accidents in 11 months. No attempt can be made to draw conclusions from this admittedly small series of patients. However, presentation of this material may be of interest.

The patients were all otherwise healthy. Their ages varied from 22 to 39 years, the average being 30 years. Gravidity ranged from i to vi; all but one patient had been pregnant at least once prior to the present complication. Only 3 patients had experienced previous pregnancy wastage: one was a gravida iii with 2 spontaneous abortions; one, also a gravida iii, had a history of a previous delivery of an anencephalic fetus at 36 weeks; and the third, a gravida iv, had had a previous missed abortion (Table I).

TABLE I. PAST HISTORY

PATIENT	AGE	GRAVIDITY	NUMBER CHILDREN LIVEBORN	PREVIOUS PREGNANCY WASTAGE
J. B.	36	3	2	None
	37	4	2	Missed abortion previous pregnancy
E. R.	30	6	5	None
I. R.	35	3	0	Spontaneous abortions, 10 and 12 weeks
E. C.	39	3	2	None
B. W.	20	2	1	None
R. S.	33	5	4	None
G. P.	22	3	1	Stillborn anencephalic fetus, 32 weeks
M. M.	31	6	5	None
A. M.	33	4	3	None
J. LaM.	24	1	0	None

Management

Symptoms of threatened abortion appeared in 8 cases in this series. These symptoms were treated by bed rest only until cessation of cramps and bleeding. At no time were hormones given. That steroid hormones can convert a threatened to a missed abortion is indicated by Hodgkinson,[7] who found this condition 8 times in 61 patients treated for threatened abortion with large doses of Delalutin or Norlutin.

Three patients had no symptoms until spontaneous termination of the pregnancy. None of the patients exhibited any of the time "dishonored" symptoms of autointoxication such as lassitude, malaise, or afternoon fever.

The diagnosis was suspected in each instance by observing a discrepancy between the size of the uterus and the duration of amenorrhea. The diagnosis became certain on further observation of failure of growth of the uterus over a period of 2 months. Only twice did uterine size reach that commensurate with a second trimester gestation. All diagnoses were confirmed by the microscopic finding of degenerated placental tissue at termination of the pregnancy. A fetus was recovered only 3 times (Table II).

TABLE II. COURSE OF PRESENT PREGNANCY

PATIENT	SYMPTOMS OF THREATENED ABORTION PRIOR TO DIAGNOSIS	DAYS BETWEEN LAST MENSTRUAL PERIOD AND FIRST SYMPTOMS OF THREATENED ABORTION	DAYS BETWEEN LAST MENSTRUAL PERIOD AND TERMINATION OF CURRENT PREGNANCY	RECOVERY OF FETUS
J. B.	Bleeding 12 days	224	256	No
	None	—	198	No
E. R.	Spotting daily 6 months	114	326	No
I. R.	Cramps and bleeding 6 days	103	178	No
E. C.	None	—	217	Yes 64 cm.
B. W.	Bleeding daily 1 month	119	199	No
R. S.	None	—	234	Yes 11 cm.
G. P.	Cramps and bleeding 3 days	82	207	Yes 1.5 cm.
M. M.	Spotting 2 days	125	225	No
A. M.	Spotting 25 days	96	191	No
J. LaM.	Cramps and bleeding 3 days	109	179	No

In each instance following diagnosis, the situation was explained to the patient. Stress was placed on the improbability of autointoxication and conservative management was advised. Surprisingly, all but one patient accepted the situation well and, with this one exception, there were no psychological problems of "carrying around a dead baby." The excepted patient became more apprehensive as time passed and a curettage was done electively 82 days after the diagnosis was made.

This management involved spending a great deal of time with each patient, listening to her, and helping her to adjust emotionally. Office visits were frequent and each patient was allowed as much time as she desired. A search was made for any bleeding tendency at each visit by determination of clotting time and observation of the clot.

None of the patients showed signs of fibrinogen deficiency by these tests, although determination of fibrinogen content of the blood was not done. All blood lost at the time of termination was found to clot well, which would indicate an ample fibrinogen supply. Two of the patients were anemic at the time of termination because of poor dietary habits.

The length of time elapsed from the last menstrual period to the termination of the pregnancy varied from 178 days to 326 days, the average being 216 days. It is recognized that the date of the last menstrual period does not always indicate the onset of pregnancy, even if the menses were regular. There were no previous periods of amenorrhea except for confirmed pregnancies. This only emphasizes the time lost from the patients' reproductive lives (Table II).

As already stated, all but one pregnancy was allowed to progress to the spontaneous onset of expulsion. When lower abdominal cramps and bleeding began, the patient was hospitalized. When the cervix was found to be dilating, evacuation of the uterus by ovum forceps and sharp curette was performed.

The one elective curettage was done in a patient with a uterus of 8 weeks' size. The cervix was rigid and exceedingly hard to dilate, while the placenta was extremely adherent and difficult to remove. Blood loss was excessive and the patient went into shock but responded to blood replacement. The hematocrit dropped from 42 per cent preoperatively to 30 per cent postoperatively.

There was no other hemorrhage and no instance of afibrinogenemia, infection, or maternal death. Blood was given to 3 other patients postabortally as replacement therapy.

Sterility following missed abortion did not appear to be a problem in these few patients. Four have given birth to normal children since the complication. In addition, one of these 4 has had a tubal pregnancy. Two patients were lost to follow-up. Three patients have had no opportunity to become pregnant since one was divorced and 2 are using contraception.

Summary

There is diversity of opinion concerning the proper management of missed abortion. Both conservative treatment with spontaneous evacuation of the uterus and surgical evacuation have their advocates.

In a personal series of 11 cases of missed abortion, 10 terminated spontaneously and the patients were then curetted. One pregnancy was interrupted by curettage. This was the only morbid patient of the group. There was no afibrinogenemia, infection, or maternal death.

No attempt is made to draw conclusions since there are so few patients. On the other hand the conservative management of missed abortion may be a good choice for the private practitioner because it is traditional and offers him protection if complications arise. This view is advanced despite the fact that valuable reproductive time is wasted.

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Discussion

DR. EDWARD A. BANNER, Rochester, Minn.—In a review of our patients Dr. Battaglino, of our fellowship staff, who is now reviewing our material for a 20 year period, found that 33 patients were classified as having had missed abortions in which intrauterine death had occurred prior to the twenty-eighth week of gestation. Eighteen patients, or 54.5 per cent, were treated by an operative procedure, while 15, or 45.5 per cent, received no specific therapy.

In the operative group of 18 cases there were 13 cervical dilatations and uterine curettages, 2 vaginal hysterotomies, and one abdominal hysterotomy. Two patients required manual removal of the placenta. In this group the total duration of pregnancy, as counted from the first day of the last normal menstrual period to the time of definitive therapy, varied from 88 to 294 days. The estimated duration of gestation prior to intrauterine death varied from 8.3 to 27 weeks. The total number of days the fetus was retained after death varied from 30 to 118 days. In this group, 14 fetuses were recovered. Four patients had received hormone therapy unsuccessfully. Two of the 18 patients had fibrinogen studies, one 8 weeks and the other 6 weeks after the intrauterine death; in both patients the results were within physiologic limits. Five of the 18 patients underwent blood transfusion. All 5 were in the group who had cervical dilatation and uterine curettage. Three of the 5 were anemic before the surgical procedure and gave a history of prolonged spotting. Five patients received antibiotics. There was no morbidity noted in the operative group. The average hospital stay was 4.6 days.

The nonoperative group consisted of 15 patients, or 45.5 per cent. All deliveries were spontaneous and were not followed by cervical dilatation or curettage. The average duration of pregnancy in this group varied from 77 to 126 days. The estimated duration of gestation prior to fetal death averaged 7 weeks, with the period the dead fetus was retained varying from 28 to 77 days, which was approximately the same as for the operative group. Five fetuses were recovered from this group. Two of the mothers had had previous hormone therapy. The results of fibrinogen studies in 2 patients were within normal limits, the studies being made 6 weeks and 7 weeks, respectively, after fetal death. There was no morbidity in this group and the average stay in the hospital was 3.8 days.

It appears that the conservative management of missed abortions would, if successful, offer the patient the least difficulty. However, under certain conditions surgical intervention may be offered with minimal risk and with satisfactory solution of a situation that is trying to both the patient and her physician.

POSTMENOPAUSAL BLEEDING*

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Part I. Changing Significance

TWENTY-FIVE years ago several studies of postmenopausal bleeding were conducted in an effort to determine the significance of this symptom, particularly as it related to the presence of malignancy. The incidence of malignancy ranged from 66.8 per cent as reported by Brown,[1] to 58 per cent as reported by Geist and Matus.[2] In 1936, one of us[3] reported upon 602 patients with the history of postmenopausal bleeding, 61.4 per cent of whom presented malignant lesions to account for the bleeding. That study was based upon patients who were 40 years or more of age, and had passed through one or more years of amenorrhea with menopausal symptoms before the onset of the bleeding.

A reappraisal of our notions concerning the clinical significance of bleeding after the menopause has been prompted by the following developments: modern education of the laity to the point at which they request more prompt investigation, the increased interest in and facilities for the early diagnosis of malignancy, the general use of exogenous estrogenic materials with subsequent postmenopausal bleeding at times, and the clinical association of certain benign conditions that might accompany or develop into malignancy.

During the period from Jan. 1, 1941, to Jan. 1, 1951, 698 patients were admitted to the Obstetrical and Gynecological Service of the Hospital of the University of Pennsylvania with postmenopausal bleeding. All were 45 years of age or more, presented menopausal symptoms of varying severity, and had been amenorrheic for a period of at least 6 months. The patients are divided into three groups depending upon the clear span, which means the period of amenorrhea before the onset of staining or bleeding (Table I). The percentage of patients with clear spans of 6 to 12 months and 12 to 24 months is about equal. While it has been customary in former studies to chose a minimum of 12 to 24 months' clear span, our experience suggested that it would be wise to limit this to 6 months. Study of the material for the present review seems to justify this attitude.

The causes of postmenopausal bleeding lend themselves to division into three major groups: those of benign origin, those due to a malignant lesion, and those in whom the cause for the bleeding was uncertain (Table II). In

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the present series the incidence of malignancy was only 30 per cent and that of uncertain cause was 12 per cent. The latter group comprises those patients for whom careful examination, biopsy, and curettage revealed no definite reason for the bleeding. This category is emphasized for two purposes: to indicate that 12 per cent of the postmenopausal bleedings presented no determinate reason and to impress the need for most careful and prolonged observation following an unsuccessful attempt to explain the bleeding. As this report progresses more details concerning the uncertain group will be brought out—such as certain constitutional values, the microscopic types of endometria, and the results of prolonged follow-up observation.

TABLE I. MATERIAL

CLEAR SPAN (MONTHS)	PATIENTS	
	NO.	%
6-12	72	10
12-24	76	11
Over 24	550	79
Total	698	100

TABLE II. ETIOLOGY OF BLEEDING

PATHOLOGIC CONDITION	PATIENTS	
	NO.	%
Benign	407	58
Malignant	208	30
Uncertain	83	12
Total	698	100

TABLE III. RELATION OF ETIOLOGY TO CLEAR SPAN

CLEAR SPAN (MONTHS)	NO. OF PATIENTS	PATHOLOGIC CONDITION		
		BENIGN (%)	MALIGNANT (%)	UNCERTAIN (%)
6-12	72	58	17	25
12-24	76	58	18	24
Over 24	550	58	33	9

The subject of the proper clear span needs clarification. In Table III the patients are classified according to the clear span in months prior to the onset of bleeding. During the first 2 spans the incidence of malignancy remained the same while it almost doubled in the last one. If the first 2 spans are grouped we find malignancy in 26 of the 148 patients. Had these patients not been investigated promptly, a prolonged diagnostic delay period would have been inevitable. As to the uncertain category, only one tenth were so classified in the over 24 month clear span as opposed to one fourth in the shorter clear spans. No doubt the latter groups include some instances of either delayed menstruation or dysfunctional bleeding, as will be pointed out later in the detailed consideration of the uncertain category.

By deleting the uncertain group the bracket is obtained in which the source of the bleeding was identified positively. Here the percentage of benign and malignant causes in relation to the anatomic area is seen in Table IV. The 234 instances of bleeding from the vagina, the vulva, and cervix—areas that are visible on routine gynecological examination—arose from malignant lesions 78 times and from benign conditions 256 times; that is, 23 per cent versus 77 per cent. However, such bleeding from the cervix alone was malignant in 26 per

cent of the instances. Indeed, the cervix comprises 31 per cent of all the malignant sources of postmenopausal bleeding in this study, despite the general notion that cervical cancer is largely a disease of the premenopause. The 15 per cent malignant source of vulvar and vaginal staining is important in light of the common delay in the diagnosis of cancer in this area. Bleeding from the uterine body was of malignant origin in 131 of 281 instances (47 per cent). The 4 adnexal lesions consisted of ovarian carcinomas, 2 of which were granulosa cell tumors.

TABLE IV. PATHOLOGIC FINDINGS IN RELATION TO SITE

SITE	NO.	PATHOLOGIC CONDITION	
		BENIGN (%)	MALIGNANT (%)
Vulva and vagina	86	85	15
Cervix	248	74	26
Uterine body	277	54	46
Adnexa	4	0	100
Total	615	66	34

TABLE V. BLEEDING OF BENIGN ORIGIN—RELATION OF SITE TO PATHOLOGIC PROCESS

SITE	TOTAL	PROCESS			
		INFLAMMATORY (%)	NEOPLASTIC (%)	TRAUMATIC (%)	EXOGENOUS (%)
Vulva and vagina	73	58	27	15	0
Cervix	184	0	51	49	0
Corpus	150	7	56	0	37
Adnexa	0	0	0	0	0

The malignant lesions consisted largely of carcinoma with several sarcomas, but the benign conditions were much more diverse in nature. The conditions that accounted for benign bleeding from each anatomic site are summarized in Table V. Of the 73 instances from the vagina and vulva, 58 per cent were mainly due to postmenopausal vaginitis and, in small part, trichomonal or monilial infections or a combination of the two. Twenty-seven per cent of the lower genital tract conditions were neoplastic, such as urethral or vaginal polyps. While these conditions may be inflammatory in origin, their polypoid appearance seemed to justify their classification as neoplastic. The lower genital tract lesions of traumatic origin were largely due to friction from pessaries and the separation of vaginal adhesions. As to the cervix, the neoplastic conditions consisted mostly of polyps. The remainder of the cervical problems were the immediate or late results of trauma such as: laceration with eversion that bled on trauma, superficial pessary ulceration, friction ulcer on the posterior part of the portio vaginalis, and a few decubitus ulcers. Here again the element of inflammation contributes but the dominant lesions seemed to fall into the groups as classified. The benign corporeal condition of inflammatory origin consisted of endometritis, sometimes with pyometra. The frequent association of pyometra with uterine cancer indicated thorough study but no malignancies were identified. The neoplastic corpus lesions were composed of endometrial polyps and submucous myomas in the ratio of 3:1.

Thirty-seven per cent of the instances of bleeding from the uterine corpus resulted from the administration of substitutional estrogenic therapy. This does not represent the true incidence of postmenopausal bleeding due to exogenous estrogens but rather that incidence in this series of hospital investigations. It is not our policy to subject all such patients to immediate diagnostic curettage.

Why then these investigative procedures? Eighteen were done for immediate diagnosis because of special circumstances such as fright to the point of hysteria on the part of the patient, worry on the part of the family (often the patient was the wife or mother of a physician), and the fact that some patients came from distant locations which made it untenable to maintain observation after institution of the customary management of postmenopausal bleeding with the history of estrogen administration. Three of the patients were habituated to estrogens with stories of periodic withdrawal bleeding. Two myomas with histories that suggested submucous tumors indicated the curettage. The remainder were curetted as the initial step in vaginal corrective surgery. No doubt some of the curettements were unnecessary but we know that only after microscopic study of the tissues justifies a negative report.

The ages of the patients who bled as a result of estrogen therapy ranged from 45 to 88 years, with 15 beyond 55 years. Of the 56 instances, 31 had experienced a clear span of more than 24 months and 7 of more than 12 years before the onset of bleeding The longest clear span consisted of 38 years. The problem of estrogen habituation will be discussed later.

In addition to the group with adequate explanations for the bleeding, there were the 83 patients for whom no definite reason was found. The investigation included both preoperative and subsequent questioning as to estrogen therapy, which was denied in each instance. Table VI depicts the distribution of the endometrial findings at the time of curettage in relation to the 3 clear spans. Inactive endometrium (''insufficient tissue'' and ''atrophic'') comprised 51.5 per cent, while active endometrium (''proliferative'' and ''secretory'') comprised 25.5 per cent. The hyperplasias (23 per cent) will be considered separately.

TABLE VI. BLEEDING OF UNCERTAIN ORIGIN—TYPE OF ENDOMETRIUM IN RELATION TO CLEAR SPAN

TYPE OF ENDOMETRIUM	TOTAL PATIENTS	CLEAR SPAN (MONTHS)		
		6-12	12-24	OVER 24
Insufficient tissue	16(19%)	1	1	14
Atrophic	27(32.5%)	9	4	14
Proliferative	17(20.5%)	7	4	6
Secretory	4(5%)	2	1	1
Hyperplasia	19(23%)	3	4	12
Total	83(100%)	22	14	47

The distribution of the inactive endometrium during the different clear spans follows: 45 per cent for the first, 36 per cent for the second, and 60 per cent for the span of 24 months or more. Such a high percentage of nonfunctioning endometrium from the shorter clear span offers additional weight to the thought that the 6 month postmenopausal interval is realistic clinically. The incidence of hyperplasia in the three eras was 14 per cent, 30 per cent, and 26 per cent, respectively. We cannot explain the presence of functioning endometrium in 7 persons more than 2 years postmenopausal nor that of endometrial hyperplasia in 12 such patients. Examples of the hyperplasia are seen in Figs. 1-5.

Patient A., 54 years of age, had a clear span of 6 years prior to the postmenopausal bleeding. The curettings appear in Fig. 1. No subsequent bleeding has occurred during 7 years of observation. This is active, functioning hyperplasia and not the burned-out senile type that persists occasionally, following the menopause.

Patient I. W., aged 55 years, bled after a clear span of 11 years. Pelvic examination was negative at the time of the curettage and the etiology of the

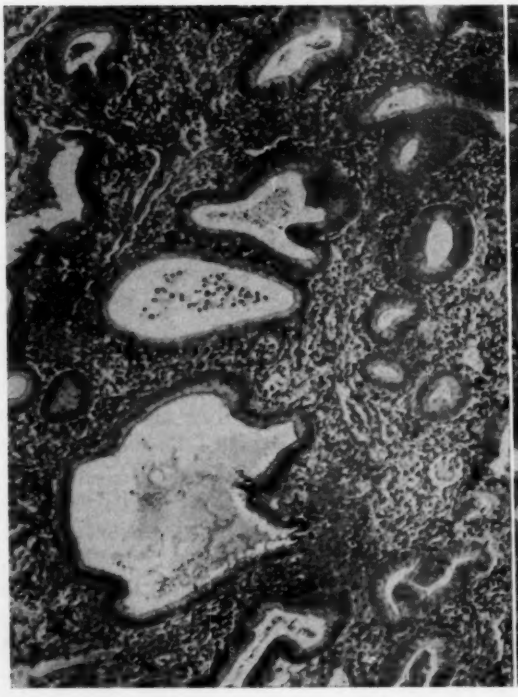

Fig. 1.

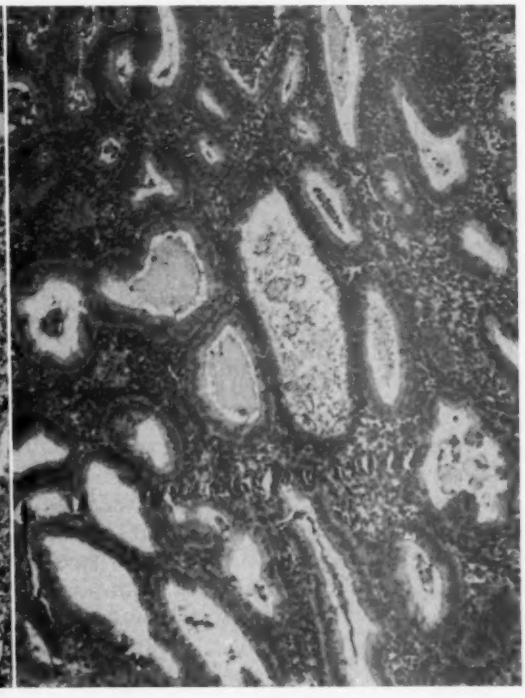

Fig. 2.

Fig. 1.—Patient A. Specimen No. 89877. Active endometrium. Hyperplasia. Six years after menopause. (×110; reduced ⅓.)

Fig. 2.—Patient I. W. Specimen No. 85885. Active endometrial hyperplasia. Eleven years after menopause. (×110; reduced ⅓.)

Fig. 3.—Patient M. W. Specimen No. 90414. Late premenstrual endometrium. Eight years after menopause. (×110; reduced ⅓.)

bleeding was described as uncertain. The curettings appear in Fig. 2. This patient died elsewhere 8 years later of ovarian carcinoma, probably granulosa cell.

TABLE VII. BLEEDING OF UNCERTAIN ORIGIN—RELATION OF FUNCTIONING ENDOMETRIUM TO AGE

ENDOMETRIUM	AGE IN HALF DECADES			
	45-50	50-55	55-60	60 PLUS
Proliferative	8	5	3	1
Secretory	1	2	1	0
Hyperplasia	2	8	5	4
Total	11	15	9	5

The actual ages of the patients with functioning endometria after the menopause are depicted in semi-decades in Table VII. All were beyond 45 and

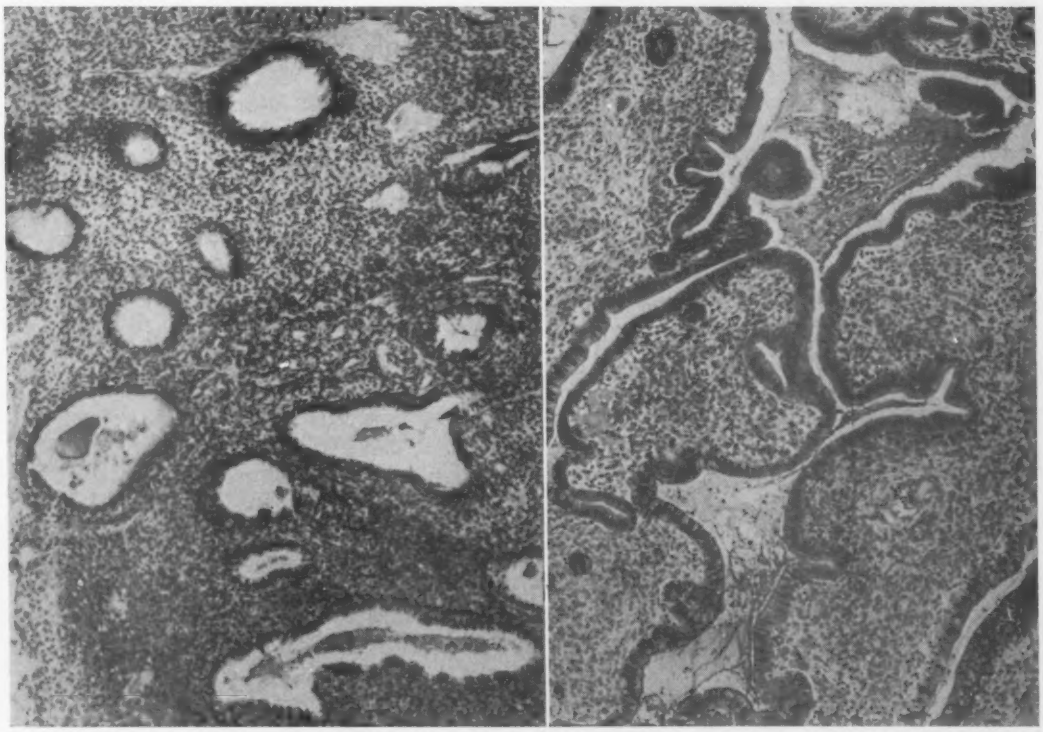

Fig. 4. Fig. 5.

Fig. 4.—Patient P. Specimen No. 27471. Stromal and glandular hyperplasia. Fourteen years after menopause. (×110; reduced ⅓.)

Fig. 5.—Patient D. Specimen No. 73074. Endometrial polyp with hyperplasia. Ten years after menopause. (×110; reduced ⅓.)

all had clear spans of 6 months or more. The oldest patient with secretory endometrium was 59 years of age and a photomicrograph of the endometrium is shown in Fig. 3. The dilatation and curettage was effective with no further bleeding during 7 years' observation.

Four patients with endometrial hyperplasia were more than 60, as follows: 62 years, 67 years, 67 years, and 69 years. Mrs. P., aged 69, with a clear span of 14 years, died elsewhere of uterine carcinoma 3 years following this curettage. The curettings appear in Fig. 4. Mrs. D., aged 67, had experienced no bleeding for more than 10 years prior to that which indicated this curettement.

The tissue (Fig. 5) showed a polyp with marked hyperplasia of both the stromal and the epithelial elements. The curettage with 2,400 mg. hr. of radium prevented subsequent bleeding but the patient died of breast cancer 5 years later. The blocks of all the endometrial hyperplasias have been serially sectioned and studied in search of malignancy, to no avail. There was no palpatory evidence at the time of the curettage to suggest a functioning ovarian tumor and subsequent developments have not indicated the presence of such a tumor, except for one instance (Patient I. W.). The entire group of patients with unexplained postmenopausal bleeding affords great opportunity for theorizing and a definite challenge as to follow-up study.

Comment

Because of several influences the significance of postmenopausal bleeding has changed. In the present study this symptom is defined as the discharge of sanguineous material from the genital tract, from 6 months forward following the cessation of menstruation at the age of 45 years of more. The cause of the bleeding was found to be benign in 58 per cent, malignant in 30 per cent, and uncertain in 12 per cent of the cases.

Although the incidence of postmenopausal bleeding due to malignancy is now approximately one half that of 25 years ago, it remains sufficiently high to require investigation. The high rate of malignancy in the early postmenopausal period, that is, the 6 to 12 month span, indicates that bleeding at this time should be viewed with grave suspicion. The presence or absence of either menopausal symptoms or menstrual molimina, the character of the bleeding, and the local findings as to postmenopausal alterations will aid in the decision regarding further investigation. Thus far office procurement of material for cytologic and tissue analysis is not dependable for the absolute exclusion of malignancy. Adequate investigation consists of the operating room procurement of specimens for both cytologic and tissue study.

Today the most frequent cause of postmenopausal bleeding is estrogen therapy. While this has never been proved to cause genital malignancy it has never been considered to be a deterrent to its development. Prior to the institution of estrogen therapy, thorough gynecologic examination is in order and this is mandatory in the event of bleeding during the administration of estrogens. A pelvic abnormality that might explain the bleeding indicates hospitalization for diagnostic and corrective measures. A negative pelvic examination indicates withdrawal of estrogen therapy and close observation. Continued bleeding in excess of 2 weeks or recurrent bleeding in the absence of estrogens should be investigated immediately.

The problem of estrogen habituation is a priori a part of this discussion. This problem gives pause to consider the possible deleterious effects of prolonged estrogenation upon the genital structures, including the breasts. There must be some physiologic purpose for the spontaneous menopause and the question arises: are we, by prolonged estrogen administration, defeating that purpose and inducing subsequent serious developments?

In clinical practice preliminary steps in the investigation of postmenopausal bleeding consist of the history, a mental surmise as to the cause, and careful examination in the effort to identify the source of the bleeding. This identification may be difficult if several possible sources are found, particularly if the examination takes place between the episodes of bleeding. The practice, fortunately less prevalent now than formerly, of deferring the examination until the bleeding ceases is to be condemned. By such practice the source of bleeding may escape detection and the diagnostic delay may be inexcusably prolonged. As to the probable areas from which postmenopausal bleeding of all

origins may arise, this study of 615 patients for whom those areas were identified suggests the order of frequency to be: vagina and vulva, 14 per cent; cervix, 40.4 per cent; uterine body, 45 per cent; adnexa, 0.6 per cent. The percentage of malignant explanations for the bleeding that arose from each area follows: vagina and vulva, 15 per cent; cervix, 26 per cent; corpus, 47 per cent. The latter figure is based upon bleeding of both uterine (277 instances) and adnexal (4 instances) areas.

The 88 patients (12 per cent of the total number) for whom no adequate reason was found to explain the postmenopausal bleeding require special consideration as to both the theoretic explanation and the ultimate outcome. In approximately one half of the patients, the endometrium was inactive, while in the remaining half, it showed evidence of persistent activity in response to stimulation with endogenous hormone. The theoretic implications will be omitted, but the follow-up data upon 77 of these patients will be presented in the second portion of this paper.

Conclusions

The incidence of malignancy to explain postmenopausal genital bleeding remains sufficiently high to require the immediate investigation of this symptom.

Early postmenopausal bleeding—from 6 months forward—should be viewed with grave concern. Should preliminary investigation not explain the bleeding, prompt, complete investigation is mandatory.

While exogenous estrogens cloud the picture concerning the significance of postmenopausal bleeding, certain rigid requirements should be observed as to preliminary examination and subsequent management in the event of supposed estrogen bleeding.

The incidence of malignancy to explain postmenopausal bleeding from the vagina and vulva, cervix, and corpus justifies utilization of every modern facility for the purpose of its prompt identification.

References

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Part II. Follow-up on 77 Instances of Indeterminate Origin

DURING the study of 698 patients who were hospitalized with postmenopausal bleeding, complete investigation failed to reveal the cause of the bleeding in 83 patients. Of these uncertain cases, 77 qualified for follow-up observation that has varied from 3 to 16 years. The remaining 6 were deleted because of: immediate hysterectomy, 3; death in 5 months from cardiovascular disease, 1; failure to follow-up, 2. Follow-up observation ranged from only 3 to 7 years in 7 patients for whom intervening death terminated the contact. In other words, 77 patients were followed from the time of the curettage either to demise or to date.

The initial operation, the type of endometrium, and the subsequent course of these patients appear in Table VIII. The endometria are divided into

three groups, depending upon the microscopic evidence of activity. The radium dosage lay slightly below or within the menopausal range. The initial therapy was effective in all but 3 of those with inactive endometria ("insufficient tissue" and "atrophic") and in all but 5 of those with active curettings ("proliferative" and "secretory"). Endometrial hyperplasia as considered in this study is, of course, active. The instances of this finding are presented separately, because of both the great interest in the subject and the subsequent developments in this particular group. Eleven were treated by simple curettage and 5 had subsequent bleeding. The remaining 7 received radium and 2 experienced recurrent bleeding. In other words, 7 of the 18 patients with hyperplasia (39 per cent) had later difficulty. In contrast, only 8 of the remaining 59 patients (13 per cent) experienced further trouble. A recounting of the difficulties, with their management, of all the patients who had subsequent trouble follows.

TABLE VIII. BLEEDING OF UNCERTAIN ORIGIN—RELATION OF ENDOMETRIUM TO OPERATION AND SUBSEQUENT COURSE

TYPE OF ENDOMETRIUM	NO. OF PATIENTS	CURETTAGE ONLY	SUBSEQUENT BLEEDING		CURETTAGE AND RADIUM	SUBSEQUENT BLEEDING	
			YES	NO		YES	NO
Inactive	40	30	2	28	10	1	9
Active	19	12	4	8	7	1	6
Hyperplasia	18	11	5	6	7	2	5
Total	77	53	11	42	24	4	20

TABLE IX. INACTIVE ENDOMETRIUM—RECURRENT BLEEDING AND SUBSEQUENT COURSE

ORIGINAL OPERATION	AGE (YEARS)	INTERVAL (YEARS)	SUBSEQUENT OPERATION	PATHOLOGIC DIAGNOSIS	FOLLOW-UP (YEARS)	SUBSEQUENT COURSE
Curettage	51	(1) 2½	Curettage	Quantity not sufficient		Good
		(2) 7	Curettage	Quantity not sufficient	10	Good
Curettage	50	1½	Curettage	Atrophy	8	Good
Curettage and radium, 1,500 mg. hr.	56	9	Curettage Plastic	Atrophy	11	Good

In the inactive group, with 3 instances of bleeding, no serious problem was encountered. The second curettings duplicated the original specimens with no recurrence of bleeding after the second curettage (Table IX). The preoperative blood pressures of these patients were 108/76, 126/78, and 170/100, respectively. This does not suggest that the bleeding was due to hypertensive disease. The remainer of the patients with recurrent trouble are divided into two groups, those with proliferative and premenstrual ("active") endometria and those with definite endometrial hyperplasia. The former category, with 5 instances of later trouble, is detailed in Table X. The interesting features are: (1) 3 "regular periods" at 6 month intervals following the curettage that revealed premenstrual endometrium at 51 years; (2) estrogen bleeding at age 55, 6 years following the menopause; (3) a curettage at 61 years for recurrent bleeding (the curettings were atrophic, with no further trouble for 9 years); (4) a total hysterectomy at 50 years in a habitual user of estrogens, so that she could continue to use this drug with no inconvenience—she developed breast carcinoma 6 years later; (5) recurrence of bleeding at 54 years of age, 7 years after 1,200 mg. hr. of radium, with no obvious reason found at the second curettage and no further difficulty.

In the latter category, with hyperplasia, 7 of the 18 patients developed subsequent bleeding (Table XI). This group includes 2 deaths from pelvic malignancy, one uterine and one ovarian, probably granulosa cell. Both may

have been present and undiscovered at the time of the original curettage. In case of the probable granulosa cell tumor the subsequent curettage with radium was conducted elsewhere. The group also includes a patient with cancer of the corpus, following two applications of radium for benign bleeding at 56 and 57 years of age. Two other interesting points are: (1) exogenous estrogen bleeding at 59, 10 years after the menopause; (2) persistent hyperplasia in 2 instances, one a year following a curettage at age 58 and the other 10 years after the original curettage with 6 subsequent clear years. The over-all picture of this table is disturbing, but the fact that 11 of the 18 patients with hyperplasia experienced no trouble following the original therapy is somewhat comforting.

TABLE X. ACTIVE ENDOMETRIUM—RECURRENT BLEEDING AND SUBSEQUENT COURSE

ORIGINAL OPERATION	AGE (YEARS)	INTERVAL (YEARS)	SUBSEQUENT OPERATION	PATHOLOGIC DIAGNOSIS	FOLLOW-UP (YEARS)	SUBSEQUENT COURSE
Curettage	51	½	0	0	8	Normal periods
Curettage	50	5	0	0	16	Estrogens
Curettage	55	6	Curettage	Atrophy	15	Good
Curettage	50	4	Total hysterectomy	Atrophy	14	Habitual user of estrogens
			Bilateral salpingo-oophorectomy			Cancer of breast 10 years later
Curettage and radium, 1,200 mg. hr.	47	7	Curettage	"Benign"	14	Good

TABLE XI. ENDOMETRIAL HYPERPLASIA—RECURRENT BLEEDING AND SUBSEQUENT COURSE

ORIGINAL OPERATION	AGE (YEARS)	INTERVAL (YEARS)	SUBSEQUENT OPERATION	PATHOLOGIC DIAGNOSIS	FOLLOW-UP (YEARS)	SUBSEQUENT COURSE
Curettage	69	3	None	None	3	Death, cancer of uterus
Curettage	55	2	Curettage and radium	Hyperplasia	7	Death, cancer of ovary Granulosa?
Curettage	56	3	Curettage	Atrophy	13	Estrogens
Curettage	46	10	Curettage	Hyperplasia	16	Good
Curettage	58	1	Curettage and radium	Hyperplasia	6	Death, cardiovascular arrest No necropsy
Curettage and radium	50	6	Curettage	Quantity not sufficient	8	Good
Curettage and radium	56	1	Curettage and radium	Benign		
		10	Attempted curettage	Cervicitis		Good, 6 months
		12	Total bilateral salpingo-oophorectomy	Cancer of corpus	12½	

TABLE XII. UNCERTAIN DIAGNOSIS—SUBSEQUENT DEATHS

CAUSE OF DEATH	NO. OF PATIENTS	AGE (YEARS)	INTERVAL (YEARS)	BLOOD PRESSURE
Cardiovascular disease	6	56 to 71	4½ to 12	182/126 160/90 120/70 190/140 155/90 142/94
Postoperative	1	69	3	154/94
Cancer of colon	1	65	4	140/78
Cancer of uterus	1	69	3	120/84
Cancer of ovary	2	63 and 64	7 and 8	164/100 130/86
Cancer of breast	2	62 and 72	5 and 9	210/110 160/105

The maximum follow-up span in this study is 17 years and the minimum 7 years, except for the intervening deaths. Three years was chosen as the least follow-up in order to include the fatal uterine carcinoma 3 years after the original curettage. In the group of 77 patients, 13 intervening deaths occurred. The span between the curettage and death ranged from 3 to 12 years. Table XII shows the causes of death. Of the 6 cardiovascular deaths, 2 occurred in the subgroup of 40 patients with inactive endometria and 4 in the division of 37 patients with evidence of endometrial function. The preoperative blood pressures in the inactive group were 182/126 and 190/140. In the functioning group, the pressures were lower. Two deaths resulted from breast cancer; one in a 62-year-old woman who habitually took estrogens, and one in a patient of 72 years whose endometrium at 67 showed extensive active hyperplasia. The uterine malignancy has been discussed previously, as has one ovarian carcinoma. The remaining ovarian cancer developed 7 years after the pelvic examination was negative and the curettage revealed atrophic endometrium, with no subsequent vaginal bleeding.

Comment

The 88 patients in whom the cause of bleeding was not identified require discussion. This study was prompted by one of us (R. W.) who, during his residency, asked the question: "What happens to these people with postmenopausal bleeding for which we can find no reason?" The number of such patients for whom records are available as to subsequent difficulty, management, and ultimate outcome affords no statistically valid answer to the question but the data do reveal certain vital points for discussion and/or emphasis.

The use of radium for treatment of postmenopausal bleeding in the absence of malignancy will be questioned. During the era in which these patients were treated the slightest gross suspicion of malignant curettings indicated the immediate application of radium with rapid paraffin section and microscopic study. The final diagnosis of malignancy led to full therapeutic dosage while that of benignancy often led to menopausal dosage. The therapeutic results of the latter plan have failed to justify its continuation. Furthermore several objections, some theoretical and some practical, to immediate intrauterine radiation have indicated a change in policy. At present, unless the curettings are highly suspicious of malignancy grossly, the radium is withheld for the microscopic diagnosis and postmenopausal bleeding of benign origin is not treated by radiation.

In further consideration of the uncertain group, the fact that simple curettage was curative permanently in 42 of 53 such patients bears emphasis. This happy result pervaded all types of endometrium except the hyperplastic. Here almost half of the patients experienced further bleeding to precipitate renewed investigation and in several instances to herald the presence of serious developments. The significance of recurrent bleeding at this age is vital. Investigation of its occurrence in a small number with inactive endometria revealed no indication for more definitive therapy than repeat curettage. The record was equally good in the active group (proliferative and premenstrual) if estrogen habituation is eliminated. This is not the case with the hyperplasia group. The development of 3 pelvic cancers (2 uterine and 1 ovarian) suggests that recurrent postmenopausal bleeding with persistent active endometrial hyperplasia implies serious developments to render mandatory both detailed investigation and definitive surgical measures. This thought is strengthened by the discovery in our laboratory (during the past 10 years) of 5 granulosa cell tumors which produced no palpable or visible ovarian enlargement. This may have been true of the patient with granulosa cell tumor herein reported, in whom 2 curettements at 2 year intervals obtained hyperplastic endometrium and who died 5 years later of ovarian carcinoma.

Fortunately only one uterine cancer seems to have escaped detection at the time of the original curettage. Recent developments in the cytologic field, particularly vaginal and endometrial aspiration with smear as the first step at the time of curettage, should increase the diagnostic achievement in the presence of early or inaccessible endometrial, as well as tubal, carcinoma. The value of this step is so definite that it should be adopted as a routine procedure in every operative diagnostic investigation of the female genital tract when the possibility of malignancy is under consideration.

Conclusions

Postmenopausal bleeding for which the original investigation reveals no explanation requires prolonged follow-up observation. Subsequent bleeding suggests repeated deliberate investigation with use of all the present-day facilities, rather than hurried, blind, and possibly inadequate surgical extirpation. If the investigation is negative for malignancy, the bleeding will respond to simple measures as a rule, except in the presence of active postmenopausal endometrial hyperplasia. Here, subsequent bleeding with persistence of hyperplasia indicates definitive surgical care. Should this become necessary, the abdominal route is preferred.

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THE HETEROLOGOUS TRANSFER OF CERVICAL CARCINOMA WITH CERTAIN HISTOLOGIC OBSERVATIONS*†

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IN THE fall of 1956 we elected to change our therapy of cervical carcinoma from the standard program of external x-irradiation followed by internal application of radon to a modification of the plan developed at Washington University.[1, 2] The latter includes parametrial injection of radioactive colloidal gold, local application of radiocobalt, and, for selected Stage I and early Stage II lesions, radical hysterectomy with pelvic node dissection.

The work reported here arose from an attempt to determine whether radical hysterectomy and lymph node dissection following parametrial radiation are valuable parts of this regime. Among the questions to be answered in this regard were these:

Is tumor tissue found at surgery in radiated lymph nodes viable? In our study of the viability of tumor tissue found in radiated nodes surgically removed, we selected growth in a heterologous host as an index of viability. Our first question may therefore be reworded:

1. Is tumor found in radiated lymph nodes transplantable?

Before this question could be studied it was necessary to answer a second question, regarding the primary tumor:

2. Can cervical carcinoma be heterotransplanted with any degree of regularity?

Finally, during the course of these investigations it was possible to obtain histologic evidence bearing on yet a third problem:

3. Are the parametria and internodal lymphatics free of tumor tissue following our regime of interstitial Au^{198} and Co^{60} therapy?

Our study suggests, though it does not prove, that all 3 questions can be answered in the affirmative: neoplasm contained within nodes is capable of growth following radiation; cervical carcinoma obtained from the primary lesion can be transplanted; and the parametria and internodal lymphatics appear to be free of tumor tissue following radiation.

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Therapeutic Regimes

During the period of this study our therapeutic regime for cervical carcinoma consisted originally of an initial parametrial injection of radiogold followed in 2 weeks by the application of radiocobalt to the cervix and fornices, with the use of a Washinton University applicator. A second similar cobalt application was administered in another 2 weeks, thus bringing total dosage to bladder and rectal tolerance as measured by a probe scintillation counter. Where possible, on the basis of the extent of the tumor and the condition of the patient, radical hysterectomy with pelvic node dissection was substituted for the second cobalt application.

Approximately 8 months after the start of the program the sequence of the first 2 procedures was reversed so that cobalt was administered first, followed in 2 weeks by radiogold. Radical surgery or a second application of cobalt was then employed as indicated after a second 2 week interval. The dosage delivered to the primary tumor, where Au^{198} was used initially, was in the neighborhood of 1,000 gamma roentgens as measured by the probe counter. The beta radiation (90 per cent of emitted radiation from Au^{198}), because of its short range, did not contribute significantly to the radiation of the tumor in the cervical area. When Co^{60} was used first, the dosage to the cervical area was roughly 10 times that delivered by radiogold.

Gamma roentgen dosages to the lateral parametrial areas were estimated by insertion of the probe counter to distort the bladder as far laterally as possible. By such measurements and calculation, these dosages generally totaled about 4,500 r after therapy with Au^{198} and Co^{60}. A given parametrial node (or internodal area) might receive somewhat more or less than this average, depending on its location, and in addition would receive a heavy beta radiation which cannot be accurately measured.

Methods

Heterologous transplant of human neoplastic tissue has been used by others for various reasons including establishment of tumor strains for research purposes and employment of transplant growth as a diagnostic index of clinical malignancy.[3, 4] The work of Toolan[5, 6, 9] suggested to us the possibility of evaluating the tumor heterograft as a technique for testing cancer viability after radiation. Before this technique could be adapted for testing the growth potential of residual tumor tissue in pelvic lymph nodes, it was necessary to determine whether or not the primary lesion in a series of cervical carcinomas could be transplanted with any regularity.

The cervical neoplasms for transplantation study were obtained from patients admitted for initial therapy during 1957. No attempt was made to transplant in situ lesions. With 2 exceptions, all tumors were squamous cell carcinomas. The distribution of cases by clinical stage is shown in Table I. Forty-five patients were subjects for this study and all lesions were transplanted at least twice. These were essentially consecutive cases of untreated cervical cancer. No attempt was made to screen out infected tumors but several early Stage I lesions with no gross tumor tissue were omitted.

TABLE I. CLINICAL STAGE OF TRANSPLANTED TUMORS

STAGE	NO.
I	10
II	18
III	13
IV	2
Adeno	2

While there has been no dearth of patients with carcinoma of the cervix, the number suitable for radical hysterectomy and node dissection has not been great. There were 12 such patients but 4 were treated prior to the beginning of the transplant project. In 2 more patients no transplantable nodes were found. The nodes from the remaining 6 patients were subjected to transplant study.

Tissue specimens were obtained just prior to the first radiation therapy and at the time of, but prior to, the second treatment. With the patient asleep, generous fragments of tumor were removed by means of a biopsy punch from the least necrotic-appearing areas of the cervix. The tissue specimens were placed in Ringer's solution containing penicillin and were prepared for injection within 15 minutes. A portion of each biopsy was fixed for permanent section and the remainder was minced with a razor to pass through a 16 gauge needle. This tumor mince was injected into the flanks of 21-day-old female rats. The animals were given heavy doses of cortisone, the total dosage

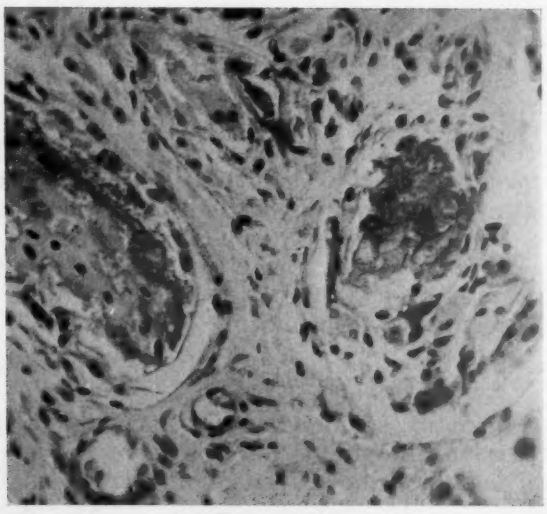


Fig. 1.—Patient No. 12, age 82. Squamous carcinoma of cervix. Negative transplant after Co^{60} therapy.

being 3 mg. of cortisone acetate given in divided doses over 8 days. Half of each group of 6 animals were sacrificed after 2 weeks and the remainder after 3 weeks. The nodules were then excised and prepared for microscopic examination. This procedure was repeated each time tissues were collected. Surgical specimens removed from node-bearing areas were examined in the operating room. All nodes were bisected, with one half being left for the histologic study and the other half being removed for transplantation.

Results

Our results with transplantation of the primary lesions are summarized in Tables II and III. Of the 45 tumors, 41, or about 90 per cent, were capable of transplantation to rat hosts either before or after treatment with Au^{198} or Co^{60}. The fact that 4 neoplasms in the two groups grew after therapy but not before reflects either inadequate biopsy material or the fact that the tumor was grossly infected. The chief problem encountered was that of local or widespread abscess formation in the rat host. Cortisone alone in the dosage used results in almost complete suppression of weight gain and the cumulative effect of cortisone and infection resulted in a mortality of about 20 per cent among the experimental animals.

Twenty-two tumors were successfully transplanted prior to low-dosage therapy with radiogold (Table II). Of these, 13 or about 60 per cent grew in the rat following this therapy. After initial treatment with radiocobalt, however, only 2 of the 15 originally transplantable tumors could be grown (Table III). This decrease in transplantability suggests an inverse relationship between transplantability and tumor dosage.

Few tumors grew luxuriantly in the 2 to 3 weeks allowed. The largest of the subcutaneous nodules attained a size of about 1 cm. Usually 3 or 4

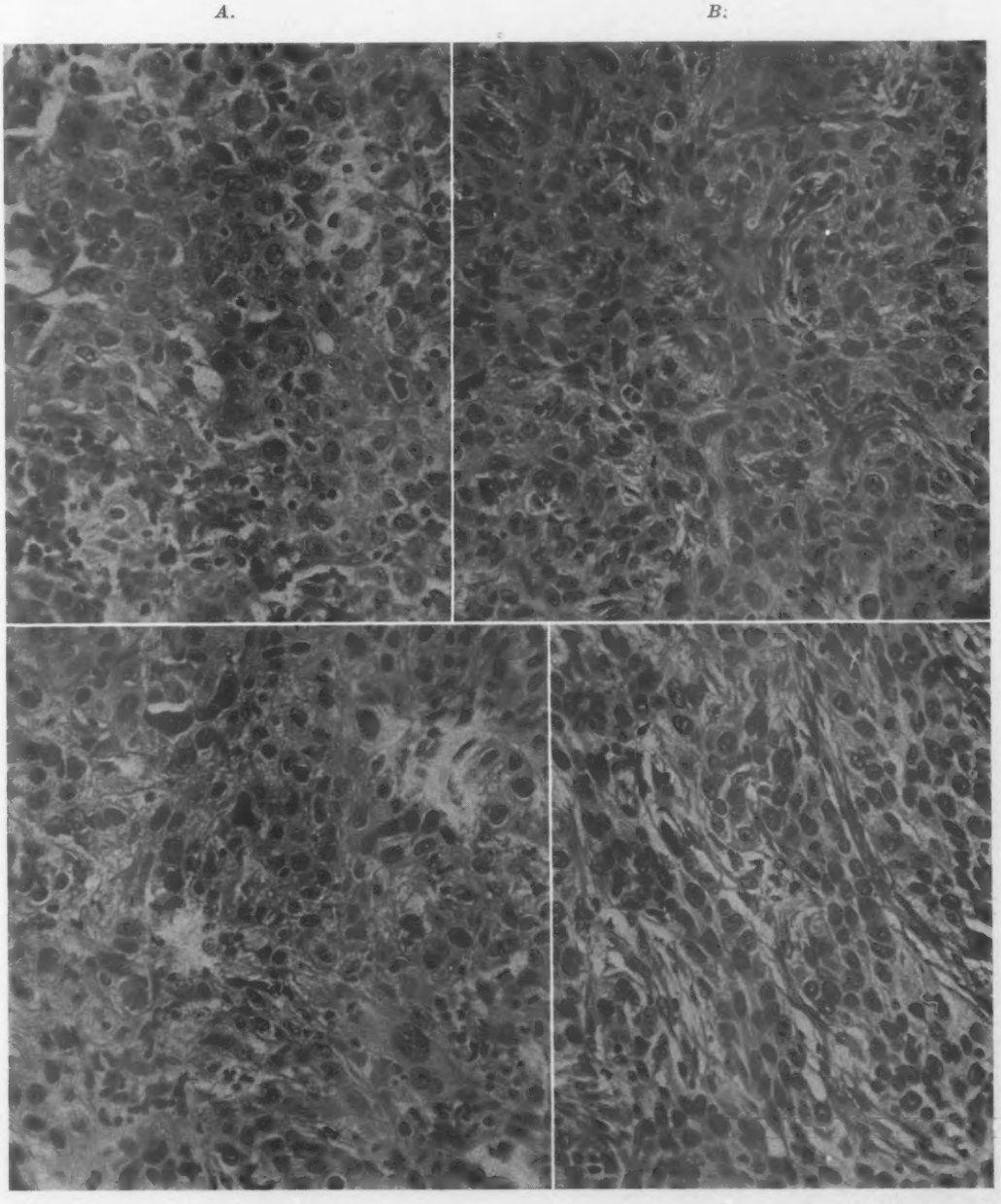


Fig. 2.—Patient No. 9, age 63. Squamous carcinoma of cervix Stage III. Anaplastic tumor. *A*, Pretreatment tumor biopsy. *B*, Pretreatment transplant. *C*, Tumor biopsy after Au^{198}. *D*, Transplant after Au^{198}.

nodules developed per rat. A variable degree of fibrous tissue reaction was present in most specimens, and vascularity varied considerably. Mitotic figures, normal staining characteristics, the gross ratio of neoplastic cells to fibrous stroma, and the total amount of neoplasm were evaluated in studying the transplants. Where only a few poorly staining malignant cells were surrounded by fibrous reaction, the transplant was judged to be in the process

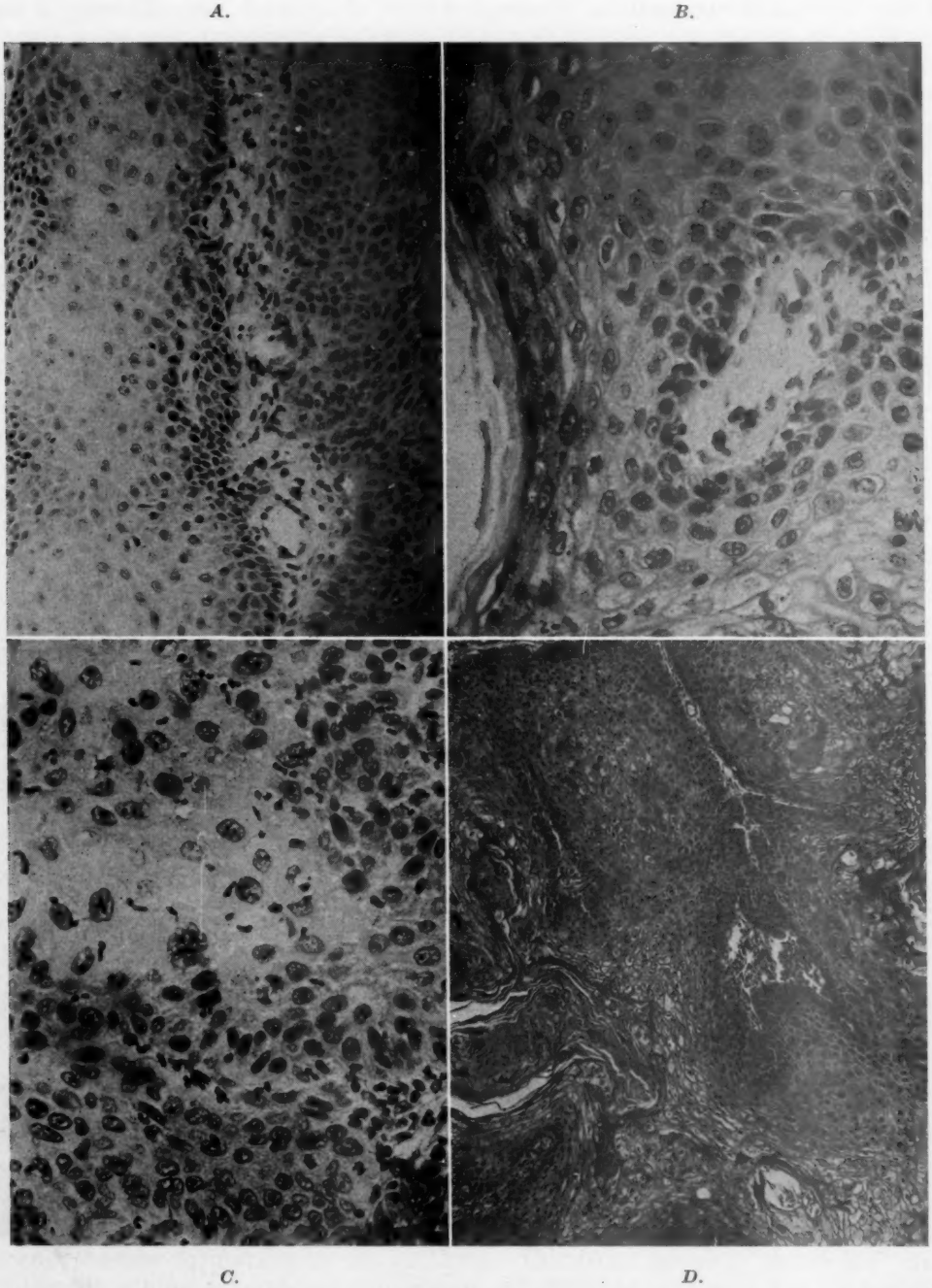


Fig. 3.—Patient No. 28, age 38. Squamous carcinoma of cervix Stage II. Highly differentiated tumor. *A*, Pretreatment tumor biopsy. *B*, Pretreatment transplant. *C*, Tumor biopsy after Au^{198}. *D*, Transplant after Au^{198}.

of resorption and was considered negative (Fig. 1). Three of the tumors were successfully subtransplanted through a second generation but no attempt was made to do this routinely or to establish "tumor strains." As noted by Toolan there were marked differences in the growth patterns of the various tumors; some grew in sheets, some in strands, and some in a cystic pattern. Several transplants increased many times in tumor volume while others grew only slightly. There was no evidence of metastasis in any of the rats.

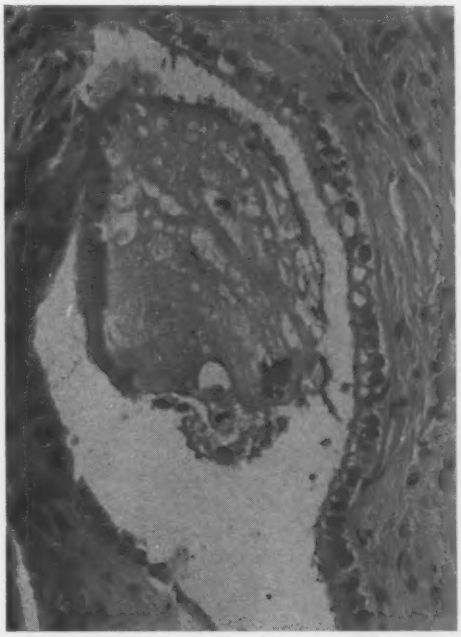
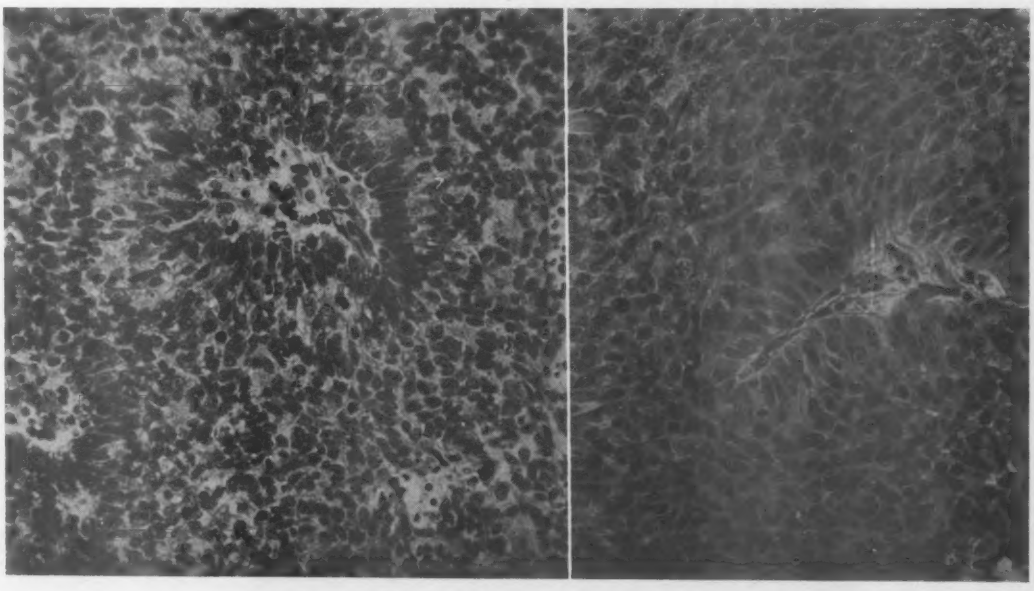
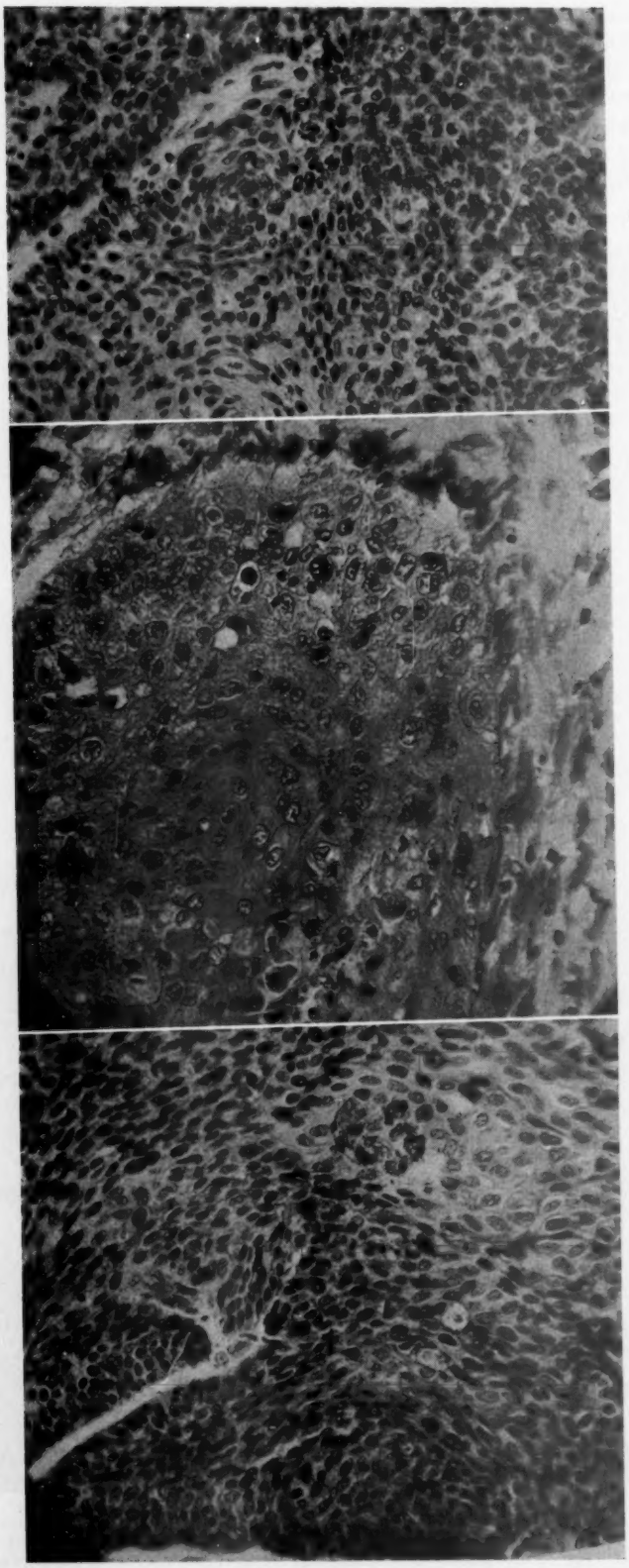


Fig. 4.—Patient No. 27, age 74. Benign cervical gland in transplant.



A. *B.*

Fig. 5.—Patient No. 37, age 55. Adenocarcinoma of endometrium with involvement of cervix. *A*, Pretreatment tumor biopsy. *B*, Pretreatment transplant.



C.

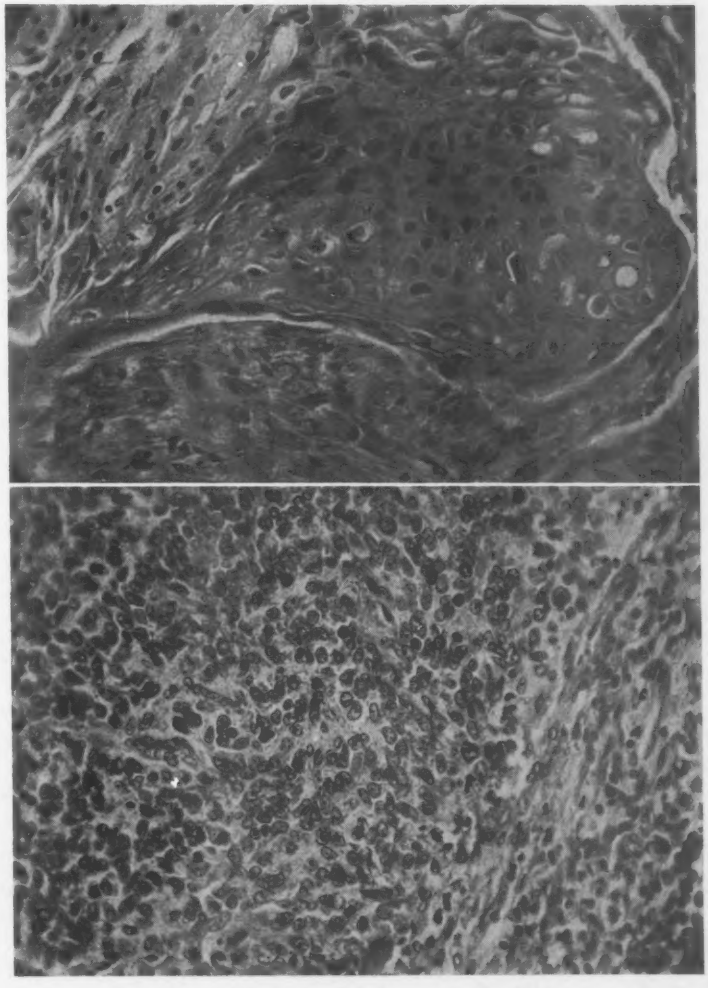
B.

A.

Fig. 6.—*A*, *B*, and *C*. *For legend see opposite page.*

Fig. 2, *A-D* shows photomicrographs of a typical anaplastic, somewhat infected tumor which grew quite well both before and after therapy. The same slight differentiation, pleomorphism, and mitotic activity seen in the original untreated tumor prior to transplantation (Fig. 2, *A*) were seen in the nodule developing in the rat (Fig. 2, *B*). The fibroblastic response in the host was minimal. Biopsy of the tumor in the patient after low-dosage irradiation with

D.



E.

Fig. 6.—Patient No. 13, age 40. Squamous carcinoma of cervix Stage I. Radical hysterectomy with pelvic node dissection. *A*, Pretreatment tumor biopsy. *B*, Pretreatment transplant. *C*, Tumor biopsy after Au^{198}. *D*, Transplant after Au^{198}. *E*, Transplant of nodal metastasis after Au^{198} and Co^{60}.

Au^{198} (Fig. 2, *C*) showed slightly greater irregularity in size of the nuclei and numbers of nucleoli. The postradiation transplant in the rat (Fig. 2, *D*) again grew well but fibrous tissue was in greater evidence.

Fig. 3, *A-D* depicts a similar sequence with a very well-differentiated tumor showing considerable keratinization. The original biopsy (Fig. 3, *A*) shows only minimal inflammation. Excellent growth in the rat is shown in Fig. 3, *B*; the tumor grew in cysts containing large amounts of keratin. The normal epithelial architecture is quite well preserved. After radiation with Au^{198} the primary

tumor had changed little (Fig. 3, *C*), but growth in the rat was, if anything, more prolific. Fig. 3, *D* shows a large nodule of active neoplasm. Mitotic figures are common; there is much keratin formation but none of the large cystic areas which were seen in the transplant grown prior to radiation.

TABLE II. TRANSPLANT RESULTS OF 27 TUMORS TREATED FIRST WITH Au^{198}

BEFORE THERAPY	AFTER THERAPY	NO. OF TUMORS
Positive	Negative	9
Positive	Positive	13
Negative	Negative	2
Negative	Positive	3
Total		27

TABLE III. TRANSPLANT RESULTS OF 18 TUMORS TREATED FIRST WITH Co^{60}

BEFORE THERAPY	AFTER THERAPY	NO. OF TUMORS
Positive	Negative	13
Positive	Positive	2
Negative	Negative	2
Negative	Positive	1
Total		18

TABLE IV. PELVIC NODE DISSECTIONS

Treated before transplant program	4	
No pelvic nodes identified at surgery	2	
Total cases not transplanted		6
All nodes negative (histologically and by transplant)	4	
Positive histologically but negative by transplant	1	
Positive by transplant but negative histologically	1	
Total cases transplanted		6
Total cases operated upon and histologically studied		12

Normal endocervical glands were found in transplants on two occasions (Fig. 4). No normal squamous epithelium was noted in transplants. The single adenocarcinoma of the cervix in this group (Fig. 5, *A*) was highly radiosensitive. Though it grew well in the rat prior to therapy (Fig. 5, *B*), it could not be found after Co^{60} therapy.

Table IV contains the data on the 6 patients treated with radical hysterectomy and studied with the transplantation technique. Positive nodes were found in only 2 of the patients. One of these, a large paracervical node, was histologically positive but did not grow when transplanted. The second positive node was detected by the transplant technique. The primary tumor was transplantable both before and after initial therapy with Au^{198} (Fig. 6, *A-D*). At the time of radical surgery no grossly suspicious nodes were found but half of all identifiable nodal tissue was transplanted. While the blocks from these nodes prepared for histologic study revealed no malignant cells, one rat transplant was strongly positive (Fig. 6, *E*). It seems likely that the greater volume of nodal tissue surveyed by the mincing technique was responsible for this positive result.

A total of 12 patients treated by radical hysterectomy and pelvic lymph node dissection were histologically studied (Table IV). Multiple blocks were prepared from all these specimens according to a prearranged scheme (Fig. 7). Particular attention was paid to the collection of the loose areolar tissue about the regional lymph nodes.

Microscopic examination of the pelvic lymph nodes revealed carcinoma in 4 of the 12 patients. In 2 of the 4 the nodal metastases were extensive and involved the common iliac nodes as well as other groups. It is unfortunate that these nodes were not transplanted because the patients were treated before the start of the transplant program. In the other 2 patients carcinoma was found in single nodes (the left obturator group in one and the left hypogastric group in the other). In none of the 12 patients was tumor tissue found outside the nodes; all internodal and perinodal tissues were free of tumor.

The primary tumor could still be identified in 7 of the 12 patients and appeared healthy in at least some areas in all. Radiation effect of some degree was seen in 5 of the 7 specimens. No tumor tissue was found in the immediately adjacent parametrial areas in any of the specimens. Three of the

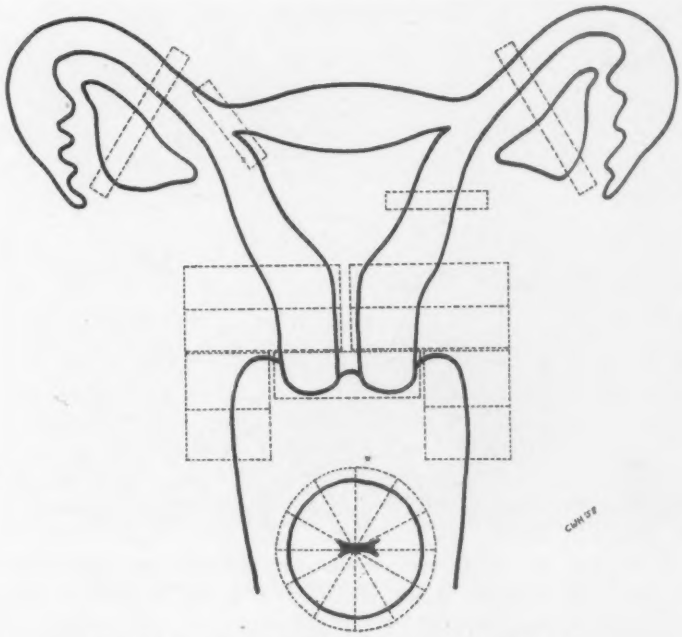


Fig. 7.—Schema of blocks for histologic study.

7 patients had nodal metastases; therefore, at least in these 3 patients, it seems probable that tumor tissue had involved or had traversed these parametrial areas prior to treatment.

Comment

While the results of our histologic studies must be considered preliminary because of the small number of patients involved, they do suggest that the likelihood of leaving behind small extranodal aggregates of cancer at surgery is negligible. We have no direct evidence that malignant cells are regularly found in such specimens, though we have noted this phenomenon in the vicinity of nodes removed at the time of radical surgery for vulvar carcinoma (Fig. 8).

The high transplantability rate of primary tumor tissues from cervical carcinoma is of interest, but perhaps even more significant is the fact that not all tumors grew equally well. A few grew extremely rapidly with the nodules

increasing to a size of over 1 cm. in 2 weeks, while others, seemingly of similar clinical and histologic malignancy, grew well but much more slowly. As Toolan[5] has noted, this behavior makes it apparent that "the criteria for malignancy of the implanted cell cannot rest upon its proliferative capacity nor even upon its transplantability." It is possible, as speculated by Toolan, that in the new host some tumor cells lose a "specific control" and thus grow to their full capabilities. In any case we regard heterotransplantability as an index of viability, not of malignancy.

Our transplanted tumors tended to reproduce their original growth patterns quite faithfully. This is a finding to be expected, especially after

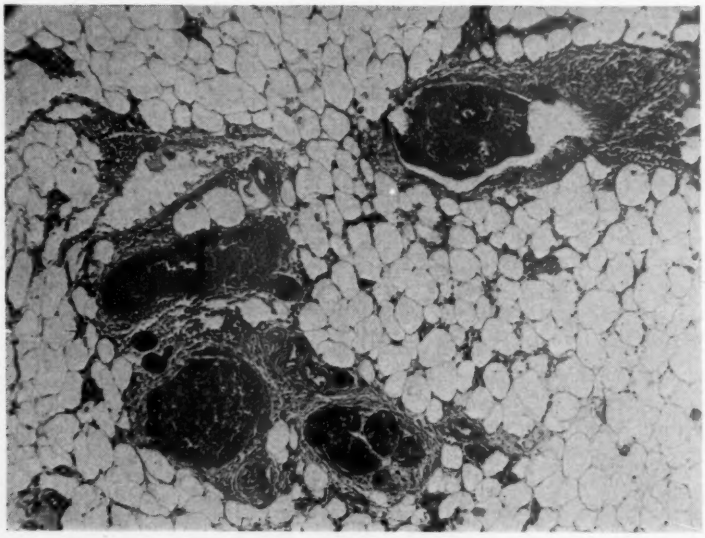


Fig. 8.—Patient D. S., age 57. Metastatic squamous carcinoma of vulva with aggregates of tumor in vessels surrounding pelvic lymph nodes.

only a single transfer.[6] The absence of metastasis in the rat host was likewise anticipated, as this has been noted previously, most recently by Skiff and associates[7] and by Fogh and Hok.[8] The failure of normal structures to proliferate in our transplants is possibly related to their "maturity"; many benign embryonic tissues have been transplanted by Toolan.[9]

The fact that metastatic malignancy is capable of heterologous growth 4 weeks following the radiation employed preoperatively indicates that such tumor is viable at the time of transplant. From our work it is impossible to determine if a more profound destructive effect might have been noted had further time elapsed between treatment and operation. The considerable growth capability required for heterotransplant does suggest that no extensive regressive changes had occurred during the 4 week interval.

It should be recalled that these data do not bear on the viability of carcinoma in pelvic lymph nodes after the greater radiation dosage given those patients considered not operable. Such patients receive in the neighborhood of 5,500 gamma roentgens (plus beta radiation) to the node-bearing areas. Presumably the viability of residual tumor tissue would be further decreased in these patients.

Summary and Conclusions

1. Carcinoma of the cervix may be heterografted into rats given cortisone. This was done in 41 of 45 patients. Transplantability decreases with increased roentgen dosage to the tumor.

2. Metastatic cervical carcinoma in pelvic lymph nodes is capable of heterotransplant following preliminary radiation—a strong indication of viability.

3. The parametrial and internodal tissues from 12 patients treated by radical hysterectomy and node dissection following radiotherapy with Au^{198} and Co^{60} were free of tumor. The significance of this finding is discussed.

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Discussion

DR. WALLACE W. NELSON, Grand Forks, N. D.—Success of transfer can be enhanced by treating animals with cortisone, antibiotics, and/or total body x-ray irradiation. Squamous cell carcinoma from most sites has been transplanted with relative ease into varied animal hosts or tissue cultures; adenocarcinoma, not so easily. We employed animals given heavy doses of cortisone and a "dip-bath" of penicillin for tissue transplants. The percentage of "takes" was high. Difficulties encountered with cellulitis and abscess formation might have been better controlled had the host animal received broad-spectrum antibiotics in addition to cortisone.

The methods we used to prepare the tissue for injection might have been refined by employing a cell suspension. The cell suspension is prepared by forcing tissue through a fine wire mesh. Reasonably equal amounts can then be injected into animals of similar age, weight, and stock. This technique would have likely allowed us to attach more significance to statements regarding rate, size, and character of growth of the implanted tissues. Even then we would be dealing with the unpredictable variations of host-tumor response—at best, hardly a matter of test tube accuracy.

Answers to the first and third questions revolve around the problem of radiation effectiveness and response. We are asked to conclude on the one hand that, in the time allotted, the radiation therapy employed has been adequate to render parametrial and internodal lymphatics free of tumor, and on the other hand that such therapy has been inadequate to sterilize regional lymph nodes. Were any internodal tissues transplanted? One node, though microscopically negative, was found to contain viable tumor.

A recent report has been made of 52 patients operated upon 3 and 4 months after having completed adequate radiation therapy by the conventional means of radium and deep x-ray. In 2, or 11 per cent, of the 18 patients who had residual tumor, this was within the internodal tissues of the cardinal ligaments. We would encourage the authors to continue the present study to convince us further that the parametrial and internodal lymphatics are indeed free of tumor following their method of radiation. Patients must first receive full irradiation therapy and then be allowed time for maximum response for us to be able to evaluate reliably viability of tumor residues.

When involved nodes are present, over-all survival results have not yet been improved by the surgical approach.

CESAREAN HYSTERECTOMY*

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THE great scientific advances in the past 20 years have favorably altered the practice of medicine and have afforded us much greater opportunities in the field of therapy. As a result, increased safety of surgery has enabled us to broaden our indications for cesarean section, and today over 50 per cent of all cesarean sections are repeat procedures.[1] Coincidentally, the question of ultimate sterilization, either for medical or for socioeconomic reasons, assumes greater importance.

The termination of the childbearing function at the time of cesarean section has traditionally involved some type of tubal surgery. However, studies have proved tubal surgery to present certain hazards and degrees of failure. Even more important is the fact that the uterus, deprived of its primary function, often becomes a distinct liability in the future over-all health picture. Since 1947, recognition of these factors has led many obstetricians to take advantage of the increased surgical safety and to recommend hysterectomy at the time of cesarean section, rather than tubal operation, for terminating the childbearing function.

Naturally, this has become a controversial issue. Opponents contend that it is a more radical procedure and that unnecessary deprivation of the menstrual function is psychologically unsound.

We believe that proper patient selection and adequate orientation (to be discussed later) not only overcome these objections but prepare the patient for a more healthful future.

Review of the Recent Literature

The first treatise on the removal of the uterus at cesarean section was by Edvardo Porro in 1876, who recommended the procedure as "a safeguard in cases of hemorrhage or other accidents at cesarean section."

With few exceptions, the literature deals with cesarean hysterectomy in obstetrical emergencies only, until about 1947, when descriptions of the elective procedure began to appear.

*Presented at the Twenty-sixth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., Oct. 2-4, 1958.

Review of the literature from 1951 to 1958 has enabled us to summarize the results of 765 cesarean hysterectomies, approximately 70 per cent of which were elective procedures. This indicates the recent popularity for this method of approach.

The uncorrected morbidity varied between 8 and 20 per cent, and it was pointed out that many of these patients were very ill on admission to the hospital. Greenhill[8] has stated that "the morbidity following 221 cesarean hysterectomies at the Chicago Lying-in was less than after ordinary cesarean section." Davis and Ward[2] reported 15.5 per cent morbidity for 1,000 consecutive cesarean sections performed on private patients.

There were 6 deaths reported (0.78 per cent) in this total group of 765 cesarean hysterectomies. None of the deaths were related to the elective procedure.

The indications for elective cesarean hysterectomy, as expressed by the various authors, are benign neoplastic disease (usually fibroids), excessive scarring of the uterus or birth canal due to a previous operation or trauma, and sterilization.

Appraisal of the literature concerning tubal sterilization reveals some noteworthy facts. In well over 30,000 cases the failure rate varied from 0.25 to 3.0 per cent, the morbidity rate from 9.1 to 22.9 per cent, and the mortality rate from 0.1 to 0.5 per cent. Especially significant are the reports that 2.5 to 24 per cent of patients undergoing tubal sterilization developed major pelvic complaints requiring subsequent operation.[6, 8, 9]

Personal Series

Our survey covers the 5 year period from Jan. 1, 1952 to Jan 1, 1957, and includes white patients at Touro Infirmary and Southern Baptist Hospital.

During this span, there were 30,889 deliveries, of which 2,323 were cesarean sections, including 101 cesarean hysterectomies. Total hysterectomy was done in 92 patients and subtotal in 9.

Age varied from 20 to 45 years, and parity from 0 to 8 (Table I). Hysterectomy for urgent reasons was done in 15 patients, while in the remaining 86 patients, the removal of the uterus was elective (Table II). Comparison of hysterectomy and tubal ligation following cesarean section is shown in Table III. It appears in our limited series that the immediate results of hysterectomy compare quite favorably with results of operations on the tubes, particularly when consideration is given the fact that 15 per cent of the hysterectomies were done for urgent indications.

TABLE I. AGE AND PARITY

AGE (YEARS)	PARITY										TOTAL
	0	1	2	3	4	5	6	7	8	?	
20-25	0	2	6	3	0	0	0	0	0	0	11
26-30	0	2	11	10	2	1	0	0	1	0	27
31-35	0	5	10	4	7	3	0	0	0	3	32
36-40	3	6	7	3	1	3	0	1	1	0	25
41-45	1	1	2	1	0	0	0	0	1	0	6
Total	4	16	36	21	10	7	0	1	3	3	101

Surgical Technique

Because of the inherent changes of pregnancy, the greater mobility actually renders hysterectomy easier in the average case. On the other hand,

identification of the cervix may be more difficult. The removal of the entire uterus is desirable since leukorrhea, bleeding, prolapse, dyspareunia, and carcinoma are complications possible when the cervical stump is left. Several methods are in use for removal of the cervix along with the fundus. One such method has been developed by the Tulane University service at Charity Hospital. When two fingers are placed through the uterine incision into the internal os of the patent cervix, the cervicovaginal junction can be palpated, usually in the region of the insertion of the uterosacral ligaments. The area is then clamped posteriorly, after which a circular incision will remove the entire cervix, as a rule without shortening the vagina. In the absence of gross pathologic indications, the adnexa are undisturbed, regardless of the age of the patient.

TABLE II. INDICATIONS FOR CESAREAN SECTION

		NO. OF CASES
Urgent (Nonelective).—		
Abruptio placentae with Couvelaire uterus		5
Abruptio placentae with "severe bleeding"		3
Placenta accreta		2
Rupture of the uterus (previous cesarean section)		4
Repeated failed attempts to deliver vaginally with forceps		1
Total		15
Elective.—		
Previous cesarean sections		58
One	19	
Two	24	
Three	11	
Four	4	
Obstruction or bleeding (fibroids, placenta previa, etc.)		17
Miscellaneous indications (varicosities, cervical stenosis, Rh incompatibility, uterine prolapse, etc.)		11
Total		86

TABLE III. COMPARATIVE RESULTS OF HYSTERECTOMY VS. TUBAL LIGATION FOR STERILIZATION AT CESAREAN SECTION

	CESAREAN HYSTERECTOMY	CESAREAN SECTION AND TUBAL LIGATION
No. of patients	101	100
Operating time	1 hour, 38 minutes	1 hour, 26 minutes
Maternal mortality	None	None
Maternal morbidity	12.5%	6%
Postoperative complications	None—96.1% Mild—2 Severe—2 (1 postpartum eclampsia, 1 hydronephrosis)	None—86% Mild—14 (cystitis, bronchitis, etc.)
Postoperative stay	5-7 days 66 8-10 days 32 11 days 1 22 days 1	4-7 days 83 4-7 days 83 9-12 days 4

It is deemed fair that consideration be given those instances where more than subtotal hysterectomy would involve undue risk or where the physician does not feel secure in performing a total removal. It is our opinion that in the desirable candidate for hysterectomy even the subtotal procedure is preferable to tubal surgery. In these cases, special attention should be given

the remaining cervix, such as adequate support, thorough cauterization or conization as needed, and periodic examination, including Papanicolaou smears.

Patient Selection for Elective Cesarean Hysterectomy

The indication for terminating the childbearing function is an important factor in the acceptability of this procedure. If neoplasm, cicatrices, or myometrial weakness is present, the patient is apt readily to accept removal of the uterus. However, if pure sterilization is advisable, or requested, it behooves the physician to evaluate the patient, particularly as to the importance she places upon menstrual function. Clear explanation to the patient and her husband is necessary, with proper stress placed on the improved outlook for the future when the useless uterus has been removed. Erroneous impressions, such as the belief that obesity, hirsutism, and frigidity are frequent sequelae of hysterectomy, should be corrected. Another question which arises stems from the fact that today we see many multiparas who are quite young. However, if we are firm in our conviction that hysterectomy has many advantages over tubal ligation, and that removal of the useless uterus offers a more healthful future, then with adequate explanation to the patient and her husband, and with their acceptance, age should not be an important consideration.

We wish to stress that should there be any reluctance or resistance to the idea of hysterectomy by the patient and her husband, the matter should be dropped and a plan of treatment more suitable to the patient adopted.

Summary and Conclusions

1. A series of 101 cesarean hysterectomies is presented and the favorable results noted.

2. A similar series of tubal ligations following cesarean section is presented.

3. Elective cesarean hysterectomy is a relatively safe procedure.

4. Proper patient selection and adequate explanation are prerequisites for this operation.

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Discussion

DR. RALPH A. REIS, Chicago, Ill.—Cesarean hysterectomy, whether urgent or elective, is not new. In 1768 Cavallini stated that "all things having been duly weighed, I do not doubt that the uterus is not at all necessary to life, but whether it may be plucked out with impunity from the human body we cannot be certain without a further series of experiments of the kind which perhaps a more fortunate generation may obtain."

As of this moment, after studying the essayists' paper rather carefully, I am not sure that this is that fortunate generation. First, we must delineate the topic under

discussion—the authors have presented an admixture of urgent and elective cesarean hysterectomies which, to my way of thinking, is the same as evaluating cucumbers and roses. Both of the latter grow on wild or cultivated plants, and at this point all similarity ceases.

So it seems with "urgent" and "elective" cesarean hysterectomies. The present series purports to be a report of 101 elective cesarean hysterectomies compared with 100 cesarean sections with tubal ligation. However, 15 were actually urgent—abruptio placentae 8, placenta accreta 2, rupture of the uterus 4, and one following failed forceps. These were, therefore, not elective. Another 17 were done for obstruction or bleeding, i.e., fibroids, placenta previa, etc., and 11 were done for miscellaneous indications including uterine prolapse, cervical stenosis, varicosities, etc. With these indicated cesarean hysterectomies no one can quarrel.

Actually, then, we can only discuss the remaining 58 cesarean hysterectomies which apparently were done for the sole purpose of sterilization. Such beclouding of the issues involved is not unique. It has occurred in every report on this subject since Davis first advocated cesarean hysterectomy. In his series, many sections were performed for medical indications, others for uterine or cervical disease, and some for women "near the end of their reproductive period." The same holds true for the Siegal and other series which the essayists quote. I therefore submit that the collected 765 cesarean hysterectomies quoted from the literature cannot be used as a basis of comparison because the "urgent" and the "elective" cases cannot be accurately differentiated. In this connection I must criticize the statement that among the 6 deaths in this group "a pulmonary embolism on the nineteenth postoperative day was not connected in any way to the surgical procedure." This I should like to debate when time is not restricted.

Of the 58 patients who had elective cesarean hysterectomies, 62 per cent had had 2 or more previous children and were 26 to 40 years of age. This means that 38 per cent were under 30, that 4 had no other child, and that 16 had had one previous child. Did the removal of the normal uterus of each of these young women with 1 or 2 children each give them "confidence in the future—an unusual sense of well-being and an improved ability to be treated with hormones?" I doubt this very much.

I have no interest in comparisons between cesarean hysterectomy and cesarean section with sterilization regarding operating time, morbidity, complications, or hospital stay. Nor do I put credence in statements that cesarean hysterectomy is "easier" and that convalescence thereafter is "easier," "smoother," "faster," "shorter." Such statements are unscientific and biased.

Now what are the facts regarding cesarean section and sterilization? Garb, in a most excellent recent review of sterilization, proves that the over-all reported failure rate for all types of tubal sterilization is 1 in 140, or 0.7 per cent, and that the only statistics of value are those following Madlener sterilization with a published failure rate of 1.4 per cent and following the Pomeroy operation with a failure rate of 0.4 per cent. All other reports are not statistically significant in his opinion, and with this I agree.

I am unable to find the figures quoted by the essayist concerning tubal sterilization. Nowhere can I find the quoted 3 per cent failure, 22.9 per cent morbidity, or the 0.5 per cent mortality rate. I would ask the essayists to enlighten me.

In a modest practice covering 37 years during which time we have relied solely upon the Madlener-Walthardt technique for tubal sterilization, we—that is, Dr. Baer, Dr. DeCosta, Dr. Gerbie, and I—have had 5 known failures. If there had been more, I am certain that either our patients or our colleagues would have hastened so to inform us. There has been during all this time no death and only the usual amount of operative morbidity.

It seems to me that an unwillingness to face an operative failure rate of 1 per cent is real evidence of medical insecurity. Would that all our operative procedures were equally successful. The occasional failure will not, in my opinion, warrant an unnecessary mutilating operation on 100 young women in order to avoid the so-called embarrassment of one failure of tubal sterilization.

AN ANALYSIS OF OFFICE CANCER DETECTION IN THE PRIVATE PRACTICE OF GYNECOLOGY*

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IT IS our intent to evaluate the results of office cancer detection when a complete office gynecological examination is performed. Similar to that of others, our concept of what constitutes a complete office gynecological examination has changed. During the past 20 years, there has been a liberalization of procedures that can safely be utilized in the office as diagnostic aids. This has resulted in additional maturity to a maturing specialty. The progress in attaining this maturity has been described by Mengert.[1] The result to the practicing physician has been an increasing potential of accurate diagnosis as well as immediate specific therapy.

We have always taken a complete history and performed a complete physical examination on all new patients. An interval history and complete physical should be routine on all repeat patients. A complete physical examination should be a head-to-toe evaluation of every patient. It should not be an examination directed only to the patient's complaint or the suspected gynecological disorder. Until 1949, an occasional office four quadrant biopsy of the cervix was included as part of the physical examination. The areas for biopsy were determined by visualized areas of bleeding or apparent friable tissue. On occasion, a Schiller test was used in an attempt to aid in pinpointing specific areas for biopsy. Black[2] reported the fallacy of depending on the Schiller test. He reported upon 2 patients with invasive lesions, one of whom had parametrial involvement. Neither had a visible lesion of the portio. Neither was detected with the Schiller test. The lesions were endocervical.

The office endometrial biopsy or endometrial sampling was not originally used. Invasion of the uterus by instrumentation, as an office procedure, implied danger. However, I wonder if complications that might occur in the patient were considered any greater than the danger to the physician's status due to professional criticism of such an office procedure.

The Randall[3] and Novak[4] curettes were described in 1935. Each author, when describing his instrument, advised that his method was valuable in

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obtaining endometrial samplings for scientific investigation of endometrium and for the study of infertility problems. Both, however, warned against the use of these instruments primarily for the diagnosis of malignancy. Thus, a more general use of these instruments in office practice has been retarded, since many physicians still hold to the authors' original limitations.

Methods

In 1949, long after many teaching clinics had established the value of the Papanicolaou smear as a screening method, we began to use it selectively in our office whenever cervical lesions were visualized. The history of this valuable contribution has been detailed in the literature and need not be repeated. The full cooperation and encouragement of the Milwaukee Hospital Pathology Department* was essential before screening procedures could be started in evaluating lesions of the cervix. Many private practitioners still face the resistance of their pathologists because of the problem of the increased work load which results from Papanicolaou screening.

Initially, our smear studies were, at times, discouraging because of the long intervals during which no malignancy was found. It was soon apparent, however, that a man-created problem was born. The problem was the fact that an occasional unsuspected malignancy was found. This made it impossible to discard screening and yet feel that adequate examination and care had been given to the patient. Rather, it became necessary to extend the use of this diagnostic aid to every new patient and every yearly repeat examination, and not use the test in selected cases alone.

By 1953, stimulated by the number of unsuspected asymptomatic cervical malignancies that had been found, we attempted to compensate for a recognized inadequacy of the Papanicolaou smear in detecting endometrial carcinoma. Having attempted, on occasion, office endometrial evaluation, we decided routinely to evaluate the endometrial cavity by office endometrial biopsy or endometrial sampling. After a number of such samplings, which were accepted by the Pathology Department with misgivings, we were encouraged to continue. It was the pathologists' opinion that the specimens were acceptable in both quality and quantity.

Though initially thought a bit unique, this idea, with modification, has been reported by Jordan[5] and Burge.[6] In their reports they refer to many pioneers who have attempted this procedure. They have adequately covered the historical background.

We have attempted sufficient endometrial samplings to form the following conclusions: (1) only rarely is the introduction of the endometrial curette or Clyman cannula impossible; (2) anesthesia is never necessary; (3) discomfort can be reduced to a minimum if the procedure and its value are explained to the patient and vigorous pressure and thoughtless handling minimized; even the routine hospital curettage, done under anesthesia, must be carefully and delicately executed; (4) the Randall and Novak instruments can be used to sound and explore the uterine cavity while curetting is done in a circumferential manner (not only is a specimen obtained, but uterine irregularities can, at times, be verified); (5) this is a diagnostic procedure; (6) it should not be used for therapy or whenever dilatation and curettage is indicated. This latter is a hospital procedure.

All specimens obtained are submitted to the hospital laboratory in 10 per cent formalin. When tissue is not obtained, as in atrophy of the endometrium

*Drs. E. Birge and D. Carlson.

in the geriatric patient, secretion is submitted to the laboratory for evaluation as endometrial Papanicolaou smears. Routine endometrial sampling along with routine cervical Papanicolaou smears became a part of every complete office gynecological examination done by our group on all private patients. Endometrial sampling, however, was restricted to all the new nonpregnant gynecological patients and to all routine repeat gynecological examinations. It was used on routine repeat examinations in women under the age of 35 when indicated by erratic bleeding or for the evaluation of infertility problems.

Our statistical report is divided into two periods (Tables I and II). The first period extends from March 1, 1949, to Sept. 1, 1953. The second period extends from Sept. 1, 1953, to Jan. 1, 1958. Prepartum and postpartum evaluation by Papanicolaou smears is absent in the first period and represents only a very small segment of the patients studied in the second period. Presently, all new obstetrical patients are given the advantage of smears unless the procedure has been done by a reputable cytopathologist during the preceding year. At postpartum evaluation, we have insisted that no therapy, such as cervical cautery, be instituted unless the result of a recent smear is known.

Results

Table III reveals the results of private office cancer detection during the two periods. During the first period, a total of 2,144 cervical Papanicolaou smears were done on 2,171 patients. During this same period, 4,259 new obstetrical and gynecological patients were examined. Testing was selective. Cervical carcinoma was detected 14 times. The ages of the patients varied between 27 and 65 years. Five of these 14 patients had asymptomatic and unsuspected lesions. Only 6 were tested with Papanicolaou smears and abnormal cells were found in all 6. The remaining 8 cervical malignancies were detected by primary biopsy or were found incidentally when operations were performed for other reasons. The in situ lesion was usually discovered in this manner. The cancer detection rate in all patients tested or found associated with other operations was 0.64 per cent. The detection rate by smear alone was a low 0.28 per cent. However, 42 per cent of the diagnosed cervical malignancies were detected initially by cervical smears.

Endometrial malignancy was diagnosed in 12 patients. All patients were symptomatic. Their ages varied between 48 and 76 years. Nine had positive endometrial samplings; one had an abnormal endometrial sampling. One had no preliminary office endometrial sampling. One had insufficient material submitted and we obtained a negative report from the laboratory. The 240 endometrial samplings done during this period were for suspected malignancy, infertility evaluation, and erratic bleeding. Endometrial malignancy was suspected and detected in 4.1 per cent of the 240 patients tested. It was present and finally verified in 5 per cent of the 240 patients who had been subjected to endometrial samplings.

Malignant lesions of other organs were found. Carcinoma of the breast was detected in 10 patients. All had nodulation; none had positive breast smears. Ovarian malignancy was found in 6 patients. All had masses verified by rectovaginal abdominal examination. One carcinoma of the vulva and one carcinoma of the Skene glands were discovered. Breast, ovarian, and vulvar lesions were all symptomatic.

Tables I to III also reveal the results of the second period. The effect of routine yearly repeat examinations is reflected in the number of procedures done as compared to the number of new patients examined during this same period. During this time, 52 cervical malignancies were detected. The ages of the

patients varied between 25 and 79 years. Of the 52 cervical malignancies detected, 18 were in situ. All 18 were asymptomatic and unsuspected. Thirty-four were invasive. Seventeen were symptomatic and unsuspected. Thirty-five or 67 per cent of the 52 cervical malignancies were unsuspected and asymptomatic. Three of the cervical malignancies, all in situ lesions, were in prepartum patients. This is an incidence of 0.7 per cent of pregnant patients tested. Proof of the status of the lesion was established by sharp cone biopsies. A re-evaluation was made 3 months postpartum. Smears have been continued at 6 month intervals. All smears have remained negative. Two of the unsuspected malignancies were found in patients who were seen for infertility evaluation. One was a 25-year-old woman with an in situ lesion. She was treated conservatively by sharp knife removal of the squamocolumnar area as a conization. Follow-up has included repeat smears. She is now pregnant for the third time. The other was a 33-year-old woman with invasive cancer. She is presently without disease 3 years after irradiation therapy.

TABLE I. CANCER DETECTION PROCEDURES CARRIED OUT

	MARCH 1, 1949, TO SEPT. 1, 1953	SEPT. 1, 1953, TO JAN. 1, 1958
Total patients tested (previous and new admissions)	2,171	6,248
Number of new patients, obstetrical and gynecological, examined	4,259	5,408
Initial Procedures.—		
Papanicolaou smears (cervical)	1,996	5,266
Endometrial sampling	226	3,681
Prepartum Papanicolaou smears (cervical)	0	211
Postpartum Papanicolaou smears (cervical)	0	641
Breast Papanicolaou smears	10	8
Total	2,232	9,807
Repeat Procedures.—		
Papanicolaou smears	148	876
Endometrial sampling	14	639
Prepartum Papanicolaou smears	–	208
Postpartum Papanicolaou smears	–	620
Breast Papanicolaou smears	–	25
Postirradiation	–	95
Total	162	2,463

The Papanicolaou smear was done in 7,822 instances during the second period. A detection of 52 cases is a rate of 0.66 per cent for all patients tested. The 0.7 per cent detection rate in prepartum patients parallels the over-all detection rate of 0.66 per cent. The question that immediately comes to mind is how many prepartum patients with unsuspected, asymptomatic cervical carcinomas were neglected because of the delay in starting routine Papanicolaou screening of the prepartum patient.

Endometrial carcinoma was treated in 29 patients. It was detected 26 times. The ages of the patients varied between 38 and 83 years. On 4 occasions, 15 per cent, it was asymptomatic and unsuspected until after office endometrial sampling. In another 4 instances spotting was minimal and it was difficult to convince the patient that office endometrial sampling, as well as hospital evaluation, was essential. In these instances relaxation of detection methods might have resulted in procrastination and delay. The insinuation of Johnson and Haynes,[12] that patients in their series of endometrial carcinoma

cases suffered from procrastination because of minimal symptoms, did not occur in our series since routine endometrial sampling resulted in establishing a positive diagnosis and made prompt treatment possible. Though all physicians should be aware of the significance and potential dangers of any spotting, patients are not. Three other cases of endometrial malignancy not diagnosed by this method were treated. The particular peculiarity of these unsuspected and undiagnosed cases will be discussed later.

TABLE II. SUMMARY OF CANCER DETECTION PROCEDURES

	MARCH 1, 1949, TO SEPT. 1, 1953	SEPT. 1, 1953, TO JAN. 1, 1958
Total procedures	2,394	12,270
Total cervical Papanicolaou smears	2,144	7,822
Total prepartum Papanicolaou smears	–	419
Total postpartum Papanicolaou smears	–	1,261
Total endometrial samplings	240	4,320
Included in the Above.—		
Combined Papanicolaou and endometrial sampling done	51	3,551
Repeat	–	639
Initial endometrial sampling done alone	175	130
Papanicolaou smear and cervical biopsy done as initial procedure	49	
Repeat Papanicolaou smear and cervical biopsy	3	
Repeat cervical biopsy	1	

TABLE III. RESULTS OF CANCER DETECTION STUDIES

	MARCH 1, 1949, TO SEPT. 1, 1953		SEPT. 1, 1953, TO JAN. 1, 1958	
Cervical carcinoma		14		52
In situ	8		18	
Symptomatic	5		–	
Asymptomatic	3		18	
Invasive	6		34	
Symptomatic	4		17	
Asymptomatic	2		17	
Endometrial carcinoma		12		29
In situ	–		2	
Symptomatic	–		2	
Asymptomatic	–		0	
Invasive	12		27	
Symptomatic	12		20	
Asymptomatic	–		7	
Breast carcinoma (symptomatic)		10		11
Ovarian carcinoma (symptomatic)		6		7
Vulvar carcinoma (symptomatic)		1		1
Hodgkin's disease of the cervix (symptomatic)		–		1
Primary Fallopian tube carcinoma (symptomatic)		1		1
Skene gland carcinoma (symptomatic)		1		–

During this period of time, breast malignancy was diagnosed and treated in 11 patients. One of these patients could very well have been the victim of procrastination had not the Papanicolaou smear of the breast secretions revealed malignant-appearing cells. All other breast lesions, clinically, indicated the necessity for biopsy and removal.

A total of 7 ovarian malignancies were diagnosed and treated. All of these patients presented with complaints. Masses were detected by rectovaginal-abdominal examinations. One vulvar malignancy was seen and treated.

Our personal experiences with the Papanicolaou smears coincide with and make up a large percentage of the cases discussed in presentations by Birge and Carlson,[7] Schulz,[8] and Schulz, Carlson, and Birge[9] in their reports of cytology at Milwaukee Hospital. These are summarized in Tables IV and V.

TABLE IV. INCIDENCE OF PROVED CERVICAL CARCINOMA

	CASES SCREENED	PATIENTS WITH CARCINOMA	
		NO.	%
1950–1952	2,170	19	0.88
1953	2,060	26	1.26
1954	3,347	28	0.84
1955	5,213	24	0.46
1956	6,829	29	0.41
1957	7,873	42	0.54
Total	27,492	168	0.73

TABLE V. STATISTICAL REVIEW OF CANCER SCREENING

	1954	1955	1956
Total patients	3,347	5,213	6,829
Total abnormal smears	301	423	232
Proved cervical carcinoma	28	24	29
False negatives	1	1	2

Table IV reveals the over-all hospital experience with cancer detection and screening. Notice the decreasing incidence of detected carcinoma in a segment of patients in whom repeat testing begins to predominate.

Table V indicates an evaluation of screening results during the years 1954, 1955, and 1956.

Note that in our private practice we have had no false negatives. False positives do not disturb us since the Papanicolaou examination is considered always as only a screening procedure. It must be verified by a cold knife complete circumferential biopsy. As an office procedure, we have successfully used the Gusberg biopsy instrument.

Comment

Any attending physician or gynecologist who utilizes the Papanicolaou method of screening patients has three responsibilities:

1. The entire value of this method depends on accurately taken and prepared smears. We use an Ayre spatula with direct application to the cervical os plus a sample from the secretion of the vaginal pool. This is immediately applied, evenly and thinly, on two slides. The physician taking these slides must always be aware that vaginitis and menopausal vaginal changes can create problems of interpretations and false positives.

2. The slides must be immersed in 70 per cent alcohol before drying and must be submitted to well-trained and interested cytopathologists for final staining and interpretation. On occasion, if the attending physician or gynecologist has been trained, is qualified to interpret Papanicolaou smears, and interprets an adequate volume of smears to retain his acuity, this procedure can be done without submitting the slides to a cytopathologist. Remember, the procedure is no better than the quality of interpretation.

3. There must be accurate follow-up of the patient so that the report, when returned to the patient, can be intelligently utilized. Adequate biopsy is

essential so that the indicated therapy can be instituted immediately. Every gynecologist has the responsibility of establishing his own office cancer detection center and his own smear and cancer registry.

An example of failure to follow a patient in this series demonstrates delay. We were unable to contact Mrs. M. S., who failed to return after a suspicious smear. Although patients are advised to return at yearly intervals, a period of 23 months and 9 days passed before she returned for a routine examination. A Papanicolaou smear repeated at that time was suspicious. Fortunately, a biopsy revealed only in situ carcinoma of the cervix. The patient was 41 years of age, a gravida iii, para iii. A hysterectomy was performed.

In only one known instance in this series did a patient with previous negative smears develop atypia. The smears were negative on Oct. 24, 1952, and atypical on Sept. 30, 1954. The smear was again atypical on Nov. 2, 1954. Biopsy done on Nov. 2, 1954, revealed in situ carcinoma of the cervix. Adequate therapy was instituted. This is also the only instance of previously negative smears later becoming positive. This is included in the hospital statistics which include 27,492 examinations. The hospital has 4 recorded false negatives, all on patients with existent cervical lesions. All had biopsies and all were treated within one month. Others have found that extensive lesions may, at times, yield negative smears if care is not exercised when the smear is taken.

The statistics of the hospital (Table IV) reveal, as previously stated, that when the same segment of the population is re-examined periodically, the number of new carcinomas of the cervix discovered by the Papanicolaou technique becomes progressively less and appears to represent the introduction of new patients into the group. From the statistics offered by the hospital and from our personal experience, we submit for consideration the advisability of spreading the interval between repeat Papanicolaou smears to 2 years. We feel this can be done with safety. It is not a problem to the physician to take smears at the presently advised yearly examination. It is not a great financial burden to the patient to have them processed yearly. Expense for this procedure is no greater than that associated with repeat chest x-rays or blood counts.

Problems related to processing Papanicolaou smears do exist. The increased work load on the laboratory facilities and personnel is one. Another results from the presently inadequate number of cytotechnicians and cytopathologists. Still another problem results from the trend toward training cytotechnicians hurriedly. Inadequate and hurried training can create great problems. The cytotechnician is adequate only to screen slides. Final interpretation must be made by an interested, well-trained cytopathologist. The aforementioned are increasing problems. If Papanicolaou smears are advocated for all women, unnecessarily, at 6 month or yearly intervals only to satisfy the patient's request, which is often stimulated by necessary cancer publicity, the problems could become insurmountable. The patient cannot be criticized. The advice and careful judgment of the physician must be relied upon. Smears are essential. The question of proper spacing is important.

Our experience with endometrial carcinoma using office endometrial sampling can be summarized by stating that, to our knowledge, in no instance was endometrial malignancy found when a patient who had negative office endometrial sampling was operated upon. The unreliability of the cervical and vaginal Papanicolaou smear for diagnosis of endometrial malignancy is again emphasized by the fact that in 17 of the patients from whom positive endometrial specimens were obtained, the smear was negative, an incidence of 65 per cent. In one it was unsatisfactory. In only 8 did the smear contain a clue. In 4, atypical cells were found. One was suspicious; 3 were positive. Abnormal cells contributed suspicion in only 30 per cent of the patients. Again, we

emphasize that endometrial sampling must be considered a screening process which is of value when positive findings occur. If office endometrial evaluation is negative but there is clinical suspicion or symptoms are present, the patient must be impressed with the necessity for hospitalization and subjected to a diagnostic dilatation and curettage.

Endometrial carcinoma can only be reflected in the cervical or vaginal pool smears, as in 30 per cent of the detected cases, when the cervix is patent and unobstructed. Stenotic closure of the cervix resulted not only in negative smears but, in 2 instances, in impossibility of probing the uterine cavity for tissue. The third case presented the problem of a cervical stump.

In these 3 instances unsuspected, undiagnosed lesions of the endometrium were found at operation. An analysis of these 3 cases follows: One patient had a prolapsed uterus which had been previously "corrected" by a Watkins interposition procedure. The Papanicolaou smear taken from the cervix was negative. There were no symptoms and it was impossible to probe the endometrial cavity because of the previous surgical procedure. The second, a menopausal woman, had a prolapsed uterus with a completely stenosed cervix. The Papanicolaou smear was negative. The third had a prolapsed "cervical stump" and a negative Papanicolaou smear. At the time of operation, a spot of blood was noticed at the cervical os. Curettement revealed endometrial carcinoma in a remnant of the uterine fundus. The patient had been told that only the cervix remained since a subtotal hysterectomy had been performed. Since then every cervical stump is gently evaluated and probed with either a Novak or Randall curette.

In our series of endometrial samplings numbering 4,560 procedures, we have had no known complications. There have been no infections. There have been no known perforations. We hurry to state that perforations have occurred in some of our hospital dilatations and curettages. In addition to malignancy, many erratic bleeding problems have been solved and, at times, corrected by the removal of various forms of benign endometrial disease during this diagnostic procedure.

Though the Papanicolaou smear and endometrial sampling have, we feel, contributed materially to the accuracy of our examinations, we would direct attention to the breast and ovarian malignancies diagnosed and treated since 1949. We sincerely feel that the real keynote of every examination, in addition to an accurate history, is a genuine attempt to perform a complete physical examination. No other physician has an opportunity comparable to that of the obstetrician and gynecologist of detecting and treating breast malignancy. Though cytology contributed to the finding of one breast malignancy, it was interrogation, inspection, and palpation followed by biopsy that made the diagnosis in the remaining 20 patients. During the period 1949 to 1958, there was one known instance where a very small breast nodule with early malignancy was missed. This was detected in about 8 weeks by a surgical colleague and subsequently removed by him.

I would also direct attention to the fact that cytology and endometrial sampling contributed nothing to the diagnosis of ovarian malignancy. Again, it was interrogation, inspection, and palpation, especially the rectovaginal abdominal examination, that created a working diagnosis which resulted in laparotomy and adequate therapy. It is, therefore, essential that a routine be established. Diagnostic aids must be employed in proper balance and associated with the intelligent complete physical examination. Some have the admirable desire and noble intention of establishing large cytological screening centers to publicize and create yearly prepaid cytological services in an attempt to eradicate malignancy. These projects have the highest humanitarian merit,

but are founded upon many errors. A complete office physical examination is a complete clinical pelvic evaluation. Cancer screening and detection should be done, but should not be an isolated procedure. A complete office physical examination must be an integral part of any cancer screening procedure.

The advisability of intelligent examination and the intelligent use of proper diagnostic aids can be emphasized by the following quotation from a presentation by another doctor. "One very important feature must be emphasized and that is the importance of early diagnosis. One hopeful sign, however, was present and that is there was a history of neglected uterine bleeding for six months or more in one half the cases. Put back the growth where it was six or even two months before the cases were operated upon and probably it would have been local in the majority of them. What we need is a prophylaxis of the incurable stage, and that can be done only by the education of both physician and patient, the former first, and to him this contribution is offered." This necessity for continuous physician education and interest, which is our responsibility as gynecologists and teachers, could not be emphasized better than it was above by Dr. John A. Sampson[10] in 1907. This program, though well-started, is only beginning to mature after 51 years.

Summary

The experience of cancer detection as it is practiced in the office of a group of gynecologists treating private patients is described. A total of 14,656 procedures on 8,419 patients are analyzed.

Conclusions

1. Though the Papanicolaou smear and the endometrial biopsy are each valuable in cancer detection, routine use of the combination when new or repeat patients are examined will aid materially in detecting the asymptomatic, unsuspected early malignancy of the cervix (67 per cent) and endometrium (15 per cent).

2. The ideal theoretical goal of eventually eradicating all carcinoma of the cervix might be considered also a possibility for carcinoma of the endometrium.

3. All diagnostic aids (Papanicolaou smears and endometrial biopsies) must be done in conjunction with a complete physical evaluation so that malignancies of other organs (breasts, ovaries, vulva, rectum) may be suspected and detected.

4. An intelligently conducted physical examination, as well as a complete history, is still the basis of the practice of good preventive and curative gynecology.

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PROPHYLAXIS OF THE POSTSURGICAL MENOPAUSE*

Estradiol Pellet Implantation

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ONE of the constant characteristics of a normal spontaneous menopause is the gradual physiologic cessation of ovarian function. This complex organic-functional regression creates imbalances within the otherwise integrated endocrine system. These imbalances are responsible for the manifestations which we identify as the climacteric or menopause.

It is not necessary to describe the menopause syndrome. As we all know so well these symptoms involve organic and functional areas. Suffice it to say that the menopause syndrome exists, it is easily recognized, and when sufficiently disabling or annoying it requires treatment. In a spontaneous menopause the endocrine and psychosomatic adjustment to decreasing ovarian function is gradual. The acute interruption of pituitary-gonadal equilibrium by surgical extirpation of the ovaries creates a precipitous imbalance by removing the source of the ovarian hormones. In an acutely induced menopause the vasomotor and nervous system evidences of this syndrome are frequently exaggerated and intense. Further, this upset is apt to be particularly severe if there has been no previous ovarian dysfunction or evidence of diminution of function. That the speed of the involutional process is responsible for the severity of climacteric symptoms is well illustrated in instances of castration during the childbearing age when the manifestations are almost invariably manifold and pronounced.[1]

The menopause syndrome is often difficult to treat when it occurs spontaneously. An acute surgical menopause is usually even more perturbing. This is true to such extent that, when ovarian function has been sacrificed, many gynecologists almost automatically prescribe estrogens parenterally or orally postoperatively.

We shall not attempt to cover the literature, but it is significant that there is accord as to the occurrence of symptoms following surgical castration. Sessums and Murphy[2] reported that 83.3 per cent of patients presented menopause symptoms within 3 months following bilateral oophorectomy; Kretzschmar and Gardiner[3] observed symptoms in 87 per cent within 3 to 7 months

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following operation and 98 per cent of Richards'[4] patients were so classified. McNair[5] noted that the maximum degree of menopause manifestations were observed within 26 to 66 days postoperatively. Delaplaine and co-workers[6] reported that most of their nontreated control patients developed symptoms requiring treatment. Grogan and Duncan[7] reported their observations in a series of 635 hysterectomies. In a group of 363 patients, in whom one or both ovaries were salvaged, 53 women, representing 14.6 per cent of the group, presented a surgical menopause necessitating substitution hormone therapy. The average age in this group was 33.8 years. These observers[7] prescribed oral estrogens postoperatively to all patients in whom bilateral oophorectomy was performed and concluded that true menopause was found to be less frequent with complete oophorectomy and a known hormonal level (substitutional) than when complete reliance for adequate control was placed upon salvaged ovaries "whose life expectancy in the absence of the uterus was likewise enigmatic." In our own experience, hysterectomy at an average age of 43 years, with nonpreservation of ovarian function and no treatment, will present flushes sufficiently severe to require treatment in 85.5 per cent of cases within one to 6 months. With preservation of ovaries 18 per cent noted flushes within 3 months.

We are not concerned here with a discussion as to whether ovaries should be removed or preserved at the time of operation. Let it be clearly understood that this discussion relates to those patients who present symptoms of acute menopause when both ovaries are removed. The problem of surgical judgment is an entirely separate area of discussion.

When the premise that the menopause syndrome is primarily the result of cessation of ovarian function is accepted, the principle of treatment by estrogen replacement is equally well established. The study herein reported was undertaken with the belief that the acute surgical menopause need not occur—that, essentially, it can be eliminated prophylactically by substitution of exogenous estrogen when the natural source is removed surgically.

Experience of Others With Subcutaneous Estrogen Implants

The ultimate goal in replacement use of hormone therapy for a prolonged period of time is an effective and therapeutic level of the administered hormone in the organism.[6]

The standard methods of drug administration, oral and injection, are not entirely satisfactory for all puposes. The frequency and the required regularity of treatment make it time consuming and often lead to lapses in therapy. Subcutaneous implantation of specially prepared pellets of estradiol, the primary follicular hormone, seems to offer some advantages. Bishop[8] in 1938 reported the implantation of estrone in a woman, with relief of menopausal symptoms. Deanesly and Parkes[9, 10] reported the "effectiveness of crystalline gonadal hormones when administered by subcutaneous implantation of solid tablets of pure substance" to mice, rats, guinea pigs, and rabbits. In subsequent observations they concluded that implantation of estradiol pellets resulted in a constant and prolonged absorption closely approximating natural secretion, and suggesting slow elaboration of the steroid material from a depot area. Bennett, Biskind, and Mark[11] in 1938 treated menopausal patients with subcutaneous estrone pellets, and noted subjective relief of symptoms within 2 weeks, which persisted for as long as 14½ weeks. Objectively, the urinary estrogen levels rose; the urinary gonadotropic hormone level was depressed, and prolonged stimulation of the vaginal mucosa occurred. MacBryde, Freedman, Loeffel, and Allen[12] treated surgically castrated women with diethylstilbestrol pellet implants. They reported complete estrogenation of vaginal

smears in 7 to 10 days, as well as associated subjective improvement. Salmon, Walter, and Geist[13] implanted crystals of estradiol benzoate in 19 menopausal patients, and 18 were relieved of hot flushes for 3 to 5 months. Okie[14] treated a series of patients with severe menopausal symptoms (both natural and surgical menopause) with implanted estradiol pellets. In all cases there was prompt relief of the menopausal symptoms, persisting for 6 to 11 months. Bennett and Te Linde[15] treated the menopause syndrome with estrogen implants and noted relief of symptoms for 3 to 65 weeks.

In 1942 Corner[16] predicted that "pellets will probably be used in human cases in which long continued action is required because of continuous absorption and avoidance of repeated injections." Greenblatt[17] expressed the opinion that implantation of estrogenic hormone pellets most nearly approaches the endogenous mechanism of hormone secretion. In October, 1949, Perloff[18] commented that "The implantation of a pellet [estrogen] in a woman at the time of panhysterectomy may possibly prevent the abrupt onset of menopousal symptoms." Brown and co-workers[19] implanted 25 mg. and 50 mg. estradiol pellets subcutaneously in women undergoing hysterectomy and bilateral salpingo-oophorectomy. Forty-five patients who had had hysterectomies previously and presented menopausal symptoms were treated by implantation of alpha estradiol. Forty-three were completely relieved of symtoms. Kupperman and co-workers[20] reported their results of implantation of estrogen pellets into the rectus muscle at time of operation. They note that "administration of pellets . . . is an effective and convenient method for controlling the climacteric symptoms of the surgical patient."

Material

In 1951 we[21] reported our observation of the first 50 patients treated with implantation of estradiol* pellets. We now report upon 150 patients who received 50 mg. pellets of estradiol implanted at the time of surgical extirpation of both ovaries. This series began in 1949 and includes only private patients operated on and observed by the authors.

These patients have been followed for at least 2 years, the range being from 2 to 8½ years. The average age of the women was 43.8 years with extremes of 30 and 52 years.

The usual gynecologic indications for laparotomy prevailed in this group. Ovarian and uterine tumors, inflammatory disease, adenomyosis, retrodisplacement, descensus, and combinations of findings were noted.

A history of menopause symptoms and flushes, tension, headache, etc., was elicited in 19 of the 150 patients studied.

Procedure

During routine closure of the abdominal wound, after the fascia had been closed, a "pocket" was made by jabbing a hemostat about 5 cm. into the subcutaneous fat at right angles to the incision and spreading the points. The fatty tissue in this region is quite avascular, and troublesome bleeding does not occur. Into this pocket two 25 mg. pellets of estradiol were inserted.

The pocket was closed with an interrupted suture, or with the fat-approximating suture if this was being employed. Closure was then completed in routine fashion. In cases of vaginal hysterectomy the pellets were implanted

*Estradiol U.S.P. (Progynon B) supplied as 25 mg. pellets in individual sterile vials through the courtesy of Dr. Edward Henderson, Schering Corporation.

laterally under the vaginal membrane. An arbitrary dose of 50 mg. of estradiol was selected because pellets of such concentration had been used in therapy of the menopause.

The manner of absorption is mainly a physical phenomenon depending on surface area exposed to the dissolving action of tissue fluids. Influencing factors are the density of pellets, size of particles comprising the pellet, and site of implantation. Subcutaneous fat is our selection as to site of implantation because absorption from fat is recognized as a slower mechanism. The rate of absorption[22] of any given amount of crystalline hormone depends on the number of pellets implanted at one time. The time that pellets continue to give off appreciable material depends on the size and weight of the pellets implanted.

Observations

With few exceptions there has been no need for supplemental hormone administration or sedation. One hundred and thirty-nine of the 150 patients have been followed. Of the 139 patients followed, only 3 presented vasomotor symptoms sufficiently disturbing to require treatment within the first 6 months; an additional 4 patients noted similar annoying symptoms between 6 months and one year postoperatively; and in 5 patients menopause symptoms aggravating enough to treat were reported during the second year after operation. Thus, 12 of 139 carefully observed patients needed supplemental hormone therapy within 2 years following pellet implantation. It is significant that over 90 per cent of the patients were symptom free 2 years after bilateral oophorectomy whereas at least the same percentage in the same average age group will present symptoms before 6 months if not treated actively.

Primary failures are those in whom symptoms appear within the first 6 months. These are attributed to fibrous encapsulation, with limited absorption. This belief is tenable because we have dissected out such pellets and on quantitative analysis find practically no diminution in amount of estradiol, hence no absorption. Also such patients obtain immediate and lasting beneficial relief from reimplantation of the pellets.

Comment

This paper is not concerned with the question of preservation of ovarian function at the time of hysterectomy. When, in the judgment of the operating surgeon, extirpation of both ovaries is necessary or advisable one can anticipate an acute surgical menopause syndrome in at least 85 per cent of the patients in the fourth decade of life. The symptomatology of this syndrome is complex and varied and needs not be discussed etiologically except that it is intimately related to ovarian function. These annoying symptoms at both functional and organic levels require early and persistent treatment. Many gynecologists recognize this occurrence to the extent that patients are placed on prophylactic oral or parenteral estrogen medication immediately after operation in an effort to maintain a normal estrogen level and ovarian-pituitary balance.

Satisfied that implantation of estrogenic pellets is therapeutically practical and effective, we directed our interest toward the control or elimination of these symptoms, which occur so frequently and so promptly after surgical extirpation of the ovaries.

Implantation of hard compressed pellets of crystalline estradiol U.S.P. results in a slow, more physiologic absorption of the hormone than any other form of estrogen administration.

The average age of the patients was 43.8 years. It is our observation, confirmed in the literature, that in such an age group one may anticipate at least 85 per cent occurrence of acute menopause symptoms after surgical extirpation of both ovaries within 6 months following operation. When 50 mg. estradiol U.S.P. is implanted in the subcutaneous fat at the time of closing the abdominal wound, these statistics are reversed. Of 139 patients observed in this series only 3 required treatment within the first 6 months, i.e., 98 per cent were in good physiologic balance. Only 7 patients needed therapy during the first year and 12 complained of flushes, headache, myalgia, tension, etc., sufficient to require estrogen substitution therapy within the first 2 years. The patients have thus been tided over a prolonged transitional phase more comparable to a well-adjusted spontaneous menopause.

The prolonged activity of the implanted pellets of estradiol is attributed to slow absorption due primarily to implantation into a bed of fat.

We have noted no local necrosis, extrusion, localized pain, or wound infection in this series. Transient fullness of the breast and mastalgia have been observed but have subsided within a few weeks. Occasionally, hot flushes were noted within the first week after operation but usually disappeared before the patient left the hospital. A most interesting observation associated with this study is the subjective progress of these patients. During the months following operation these women report an excellent sense of well-being. Disturbing postoperative sequelae which, although not serious, certainly do not enhance postoperative well-being, need not occur. There is a more balanced return to a normal place in society than is frequently noted following this type of surgery. This is an intangible functional response which is most real and which is worthy of note.

The only contraindication to pellet implantation is the presence of the uterus. Should both ovaries be removed and the uterus left behind, implantation of estrogen may be followed by prolonged bleeding.

Summary

1. A series of 150 patients in whom both ovaries were extirpated at the time of hysterectomy is reported. One hundred and thirty-nine of these patients have been followed for from 2 to 8½ years.

2. Hard compressed pellets containing 50 mg. of estradiol U.S.P. were implanted into the subcutaneous fat during closure of the abdominal wound.

3. Implantation of pellets is a simple procedure.

4. Implantation of estradiol U.S.P. pellets offers a means of prolonged and continuous slow absorption of estrogenic hormone.

5. At an average age of 43.8 years, 98 per cent of the patients so treated were subjectively free of acute postsurgical menopause symptoms during the first 6 months, and 90 per cent were symptom free 2 years following operation.

Conclusion

Implantation of estradiol U.S.P. at the time of surgical extirpation of both ovaries is suggested as a satisfactory means of prophylactic elimination of the surgical menopause.

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Discussion

DR. HAROLD C. MACK, Detroit, Mich.—In a large series of clinical trials the authors have demonstrated clearly the efficacy of estradiol pellet implantations for the prevention of symptoms of the surgically induced climacteric. As shown in previous reports in which other estrogen pellets were implanted subcutaneously, it seems clear that such depot deposits are not only effective but are also well tolerated by the majority of patients. Since the women in this study ranged in age from 30 to 52 years (average, 43 years) it seems evident that at the time of castration a large proportion must still have had active ovarian function. Hence, many, if not most, were destined to experience varying degrees of acute withdrawal symptoms requiring therapy.

Despite this evidence that the routine employment of the authors' method appears to be highly effective and apparently innocuous to date, several questions should be asked before it can be recommended for adoption:

1. Is routine "prophylactic" therapy of climacteric symptoms necessary or desirable before it is established that the symptoms will occur?

2. Is not the chief purpose, as well as advantage, of this method one of convenience in minimizing the need for individualized supportive management of the menopause?

3. Is it a sound policy to subject all castrated women routinely to the same large dose of estradiol which is capable of producing breast stimulation or prolonged bleeding if the uterus were retained?

4. Is unopposed, continuous, unphysiologic stimulation by a potent anabolic agent actually without harm?

In my own experience (which does not include routine prophylactic oophorectomy) the incidence of severe symptoms not readily amenable to therapy by any of the many oral estrogen preparations is not impressive. True, some patients with greater degrees of emotional instability are more difficult to manage than others. They require strong emotional and estrogenic support. Most, however, are readily controlled by more modest doses of estrogens, by simple tranquilizing agents, or, many times, by reassurance alone.

The routine prophylaxis of flushes that may never occur impresses me as similar to routine prophylactic administration of antibiotics when no infection is present. We have all seen serious consequences of the latter. There is reason to suspect also that prolonged,

continuous administration of a potent anabolic agent such as estradiol may have undesirable effects upon the endocrine system and upon other end organs. In a discussion of untoward results of prolonged, uncontrolled steroid therapy from stimulation of the breasts and pelvic organs, Masters, like others, has warned against the "possible carcinogenic effects of the sex steroids on these target organs." In the first session of this meeting, Dr. Payne cited the case of a woman who used estrogen habitually and who developed mammary carcinoma after surgical castration. Coincidence? Perhaps, yes—perhaps, also, no!

Finally, one might also hesitate to indorse this technique in fear that uncritical readers may embrace it to further justify routine prophylactic oophorectomy. I am happy to add that the authors do not here advocate this practice.

I trust that these critical comments on an eminently effective technique are not construed as complete condemnation of a thought-provoking paper. My intention is to arouse caution and to plead for patient, individualized, controlled therapy based upon actual need, rather than intensive, uncontrolled routine treatment of potential symptoms which, however disagreeable, are not diseases.

CERVICAL PREGNANCY

Review of the Literature and Presentation of Cases*

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RUBIN,[1] Studdiford,[2] and Schneider[3, 4] have each presented major discussions of the interesting problem of cervical pregnancy. Other authors discussing this topic, in this century, have primarily concerned themselves with the case report type of presentation.

Rubin accepted 7 cases to the year 1911 (all German language references) as proved instances of cervical implantation and then presented a case of his own. He cited four criteria which must be present to demonstrate a "genuine cervical placenta." These criteria were: (1) there must be cervical glands opposite the placental attachment; (2) the attachment of placenta to cervix must be intimate; (3) the whole or a portion of the placenta must be situated either below the entrance of the uterine vessels or below the peritoneal reflection on the anterior and posterior surfaces of the uterus; (4) fetal elements must not be present in the corpus uteri.

Rubin stated that in certain of the "older cases" the diagnosis of cervical pregnancy had been made by digital examination and a portion of the placenta had been "felt to be attached to the cervical mucosa." Such observations, he warned, were very likely to be deceptive.

Thirty-four years later, Studdiford concerned himself with this entity in a masterful "partial review of the literature" and reported 2 probable cases. His introduction began with the notation that "only one report of this condition can be found since 1900 in the journals of this country." He commented, however, on the rather abundant literature in foreign publications relating to this condition.

Studdiford divided all of the published cases to that date (1945) into two groups. The first of these included instances of cervical pregnancy supported by pathological evidence and the second group comprised those in which such

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a gestation was diagnosed on clinical evidence. He emphasized that both of these categories were to be sharply differentiated from the isthmicocervical pregnancies described by Aufeld and Aschoff.

Fourteen cases were included by Studdiford in his "proved group" and in 12 of these, the relationship of the placenta to the cervix was "established beyond doubt" by pathological examination of the entire uterus obtained by operation or postmortem examination. There was nothing in the history of these 14 patients, except that they belonged to an older age group, to suggest any etiological factor other than chance. He stated that only one case (Tarnier's) had developed to term. The commonest symptoms were vaginal bleeding which tended to become more profuse, vague lower abdominal discomfort, backache, and occasional disturbance of urination. A history of painful, expulsive uterine contractions could not be obtained in these cases. The diagnosis most often entertained was early or late abortion. Other erroneous diagnoses that had been made included early placenta previa, cervical neoplasm (2 instances), and ruptured ectopic pregnancy. Four of the 14 patients failed to survive—a mortality of 30 per cent. It is striking to note that transfusion was not utilized in this group.

Studdiford, in discussing the pathological findings in these patients, stated that "in all of them, the placental implantation *appeared** to be confined to the cervix." However, owing to the fact that preliminary operative procedures had been utilized at varying intervals before the removal of the uterus, in only one instance was the specimen intact. This was a pregnancy of 22 weeks' duration treated by immediate total hysterectomy.

In the second (clinical evidence only) group of cases (also numbering 14) Studdiford virtually excluded 4 cases as being too scantily documented. He felt, however, that there were certain cases in which one had to accept the clinical observations of those who reported the cases. The maternal mortality for the "nonproved" group was 10 per cent. In both groups of cases combined, the mortality was found to be a little more than 20 per cent. Transfusion was used only one time in the latter group.

Both of the cases reported by Studdiford would certainly be regarded as presumptive in 1958. He asserted that these cases were cervical pregnancies only because of his careful examination of the endocervix. He simply stated that the placenta was attached to the endocervix and noted the presence of a small contracted fundus above the cervix. He had no pathological data to substantiate either of his cases. In both instances, manual and instrumental removal of the conceptus and/or tamponade was the only treatment required. Studdiford was of the strong opinion that many cervical pregnancies terminated in abortion at a very early stage because of the unfavorable site of nidation, and so escaped recognition.

Schneider[3] has written extensively on this subject and has established the most rigid criteria. In 1946, he stated that 12 cases of "distal ectopic pregnancy" (implantation of the ovum in the cervical mucosa) had been proved

*Italics by the present authors.

to that date, including his own. His case, presented in 1946, was treated by dilatation and curettage. Five weeks later the cervix appeared normal. He found decidual cells in the endocervical stroma but no chorionic villi. Schneider listed 4 entities to be considered in differential diagnosis: incomplete abortion, cervical abortion, tumor, and bleeding varicose veins of the portio. Schneider felt that the first case of Studdiford was to be regarded as an instance of a corporeal and cervical pregnancy. He felt that Studdiford's second case represented a fairly certain case of cervical implantation because rupture of the cervix into the vaginal fornix occurred.

Schneider emphasized that the histological examination of a case of intact cervical pregnancy in an early stage is still lacking. He stated "the more distally in the cervix the pregnancy is located and the earlier the time it comes to our attention, the more convincing and simple is the proof of cervical implantation." He was most insistent that a true cervical pregnancy may be said to exist only if the placentation is completely and exclusively limited to the cervix, and that cases dated beyond the third month of gestation could not possibly be considered "proved cases" since the isthmus by this time is inevitably involved in chorionic invasion. He felt that most of the cases recorded to that date in the literature were to be placed in the category of "corpus-isthmic-cervix placentas."

He summarized his position in 1946 by stating that in extirpated or postmortem specimens, microscopic evidence of the cervicoisthmic boundary was indispensable for the diagnosis of cervical pregnancy. However, in the case of an early pregnancy situated in the distal portion of the cervix and accessible to clinical exploration, the presence of an intact upper portion of the cervicoisthmic canal would be sufficient for diagnosis.

In 1957, Schneider would accept only 17 cases as instances of placentation restricted to the cervix. He reiterated his contention that only those cases in which the placentation is restricted to the cervix distal to the "os internum histologicum cervicis uteri" should be called proved distal ectopic pregnancies, primary cervical pregnancies, or genuine cervical pregnancies. He again emphasized that no pregnancy older than 12 weeks was amenable to anatomical proof.

He observed that "cervical pregnancies which are not acceptable as primary because they have transgressed into the isthmus or into the isthmus and corpus are even *more important** from the clinical point of view." They constitute the majority of reported cervical pregnancies because they represent gestation in a further and more developed stage and are accompanied by even more dreaded and formidable symptoms.[11] Schneider emphasized that a well-developed *decidua* existed only in the corpus in contrast to the *decidual reaction* which may occur in the vicinity of the ectopic implantation.

Certain attitudes and observations concerning cervical pregnancy published in this decade require tabulation. Duckman[5] presented a case in which

*Italics by the present authors.

placental tissue was removed from the cervical canal with ease and was unaccompanied by hemorrhage. Duckman concluded that numerous early cases of cervical pregnancy remain undiagnosed because of expectant therapy in the majority of abortions. He contended that it was possible to diagnose clinically an early cervical pregnancy in the absence of severe hemorrhage or strong placental attachment. Such a diagnosis, however, should require: (1) a dilated thin-walled cervical canal containing histological evidence of the products of conception; (2) a patulous external cervical os; (3) a small, firm uterine body with a normal-sized internal os "resting on top" of the dilated cervix.

Baptisti[6] reported a case in which the bleeding was moderate but not frightening. A single bottle of blood was given. In his second case, bleeding was more severe but packing of the uterovaginal canal controlled the hemorrhage. He also cited 3 cases reported by Billingson in which bleeding was not excessive. Baptisti felt that 17 cases of cervical pregnancy had been listed since Studdiford's review. In this group transfusion was required in 9 patients and one death occurred.

Hennessy[7] restated Rubin's criteria for diagnosis and presented a case requiring hysterectomy. The pathologist reported placental tissue with villi implanted in the cervix and decidual tissue only in the uterus.

Flanagan and Walsh[8] felt that cervical pregnancy follows a rather typical pattern which they listed as follows: (1) cases usually terminate spontaneously during the first trimester; (2) correct diagnosis is rarely made before examination under anesthesia; (3) vaginal bleeding, usually painless, is invariably the primary symptom; (4) there is usually profuse hemorrhage from the site of cervical implantation on any attempt at removal.

Their case differed from this pattern only in that there was very little bleeding at operation. The treatment in their patient consisted of finger curettage and extraction of the mass with placental forceps. They felt that minimal bleeding occurred in their case because surgery took place 3 to 5 days after death of the fetus. They postulated that decidual necrosis had occurred and a line of cleavage between the endocervix and the secundines had formed with thrombosis of the end vessels. These authors also felt that the occurrence of cervical pregnancy is more frequent than is realized.

Greenhill[9] showed a photograph of one of his 2 cases (not reported). This is a truly remarkable illustration showing a transverse section through the uterus. The entire conceptus lies attached in the endocervical canal below the anatomical internal os. This would seem to be as totally proved an instance as has ever been recorded.

Lloyd[10] reported a case which he felt brought the total reported cases to 52 (September, 1957). This figure is to be noted in contradistinction to Schneider's more severe analysis (January, 1957—17 cases). In Lloyd's case there was no overwhelming bleeding and it could not be proved pathologically. He commented "it is certainly much to be desired to secure confirmation from the pathologist for one's diagnosis but such is not the sine qua non in most conditions any more than in lobar pneumonia."

Duckman and Amico[11] discussed cervical abortion (the cervical stage of a spontaneous abortion of an intrauterine pregnancy) which they felt to be more frequent than cervical pregnancy but stated that the incidence is difficult to obtain. These authors presented the following criteria to aid in the differential diagnosis of cervical abortion and cervical pregnancy: (1) the corpus that surmounts the distended cervix is usually larger than normal in a cervical abortion (in an early cervical pregnancy the corpus is relatively small); (2) in a cervical abortion, the internal os is dilated as well as the external os but in cervical pregnancy, the internal os is practically closed; (3) in a curettage of a cervical abortion, the placental tissue can be palpated extending from the cervical canal through the internal os and attached to the uterine canal; (4) finally, until a stage of cervical abortion is well advanced, the external os is usually closed in a cervical abortion because it is this resistance to dilatation which is responsible for the cervical abortion; however, in a cervical pregnancy, the external os is usually partially dilated.

Case Reports

We have reviewed the records of the two hospitals with which we are affiliated for the 10 year period ending July 1, 1955. During this period (excluding therapeutic abortions), 47,974 pregnancies have terminated in these two institutions: 44,347 term or premature deliveries, 3,353 spontaneous abortions, and 269 tubal pregnancies. Five diagnoses of cervical pregnancy have been entered in the files of the record rooms. We will present these 5 cases and subsequently discuss the justification for these diagnoses.

CASE 1.—A 47-year-old gravida ii, para i, entered the hospital April 28, 1952, because of vaginal bleeding. Her last menstrual period had begun Feb. 19, 1952. A 2 day episode of vaginal spotting had occurred 3 weeks prior to admission. On the day before entry bleeding occurred again and gradually became more severe. The patient had also experienced mild low back pain. Past history was noncontributory.

Upon admission, general physical examination was negative. There was no evidence of shock. Routine blood counts and urinalysis were within normal limits.

Pelvic examination under anesthesia was performed. A large boggy cervix, approximately 7 cm. in length and 6 cm. in diameter, was palpated. The fundus was somewhat softened and only slightly enlarged. No adnexal masses were palpated. The external os was extremely blue and the intensity of the color was comparable to that of methylene blue. The obstetrician suspected a cervical pregnancy, and performed a dilatation and curettage. Several pieces of placental tissue were removed from the cervical canal. Only decidual tissue was found in the endometrial cavity. The endocervical canal was biopsied and thoroughly curetted. The bleeding was profuse. The postoperative diagnosis was "cervical pregnancy." The patient made an uneventful recovery and was dismissed from the hospital May 1, 1952.

The pathological report showed: "retained placental tissue attached to hemorrhagic endocervical tissue."

CASE 2.—A 35-year-old gravida ii, para i, was admitted to the hospital April 17, 1951, because of severe vaginal bleeding. Menses had been regular until 3 months prior to entry. Since that time vaginal spotting or bleeding had occurred each day. This became progressively more severe in the 3 days prior to entry.

The patient had had an appendectomy in 1941 and lysis of adhesions for partial bowel obstruction in 1951.

Physical examination showed a pale-looking woman, who was not acutely ill. Blood pressure determination was 110/70 mm. Hg. Pelvic examination revealed "a large, dirty-gray, fungating lesion which appears to have replaced most of the cervix, with profuse bleeding coming through the mass." Urinalysis was negative. The hemoglobin determination was 8.6 Gm. per cent. The erythrocyte count was 3.8 million per cubic centimeter. It was the operator's opinion that the lesion was an advanced cervical carcinoma.

After a 500 c.c. transfusion of whole blood was started, the patient was taken to the operating room. A few small pieces of tissue, "which looked malignant on gross examination," were removed from the cervix. The cervix was then sutured at 3 and 9 o'clock to ligate the cervical branches of the uterine arteries. The uterus, cervical canal and the vagina were packed with gauze. The patient was returned to her room in "fair condition." She received a second transfusion after the operation and in the next 48 hours was given an additional 1,000 c.c. of whole blood.

The pathologist reported "partially organized blood clot, decidual tissue, and chorionic villi in cervical tissue. There are no atypical elements present."

The patient was then referred to a gynecologist who returned her to the operating room April 19, 1951. At this time, the endometrial cavity was thoroughly curetted and no tissue obtained. The endocervix was then curetted and what appeared grossly to be placental tissue was removed. The cervix was biopsied at several sites by removing wedges of tissue through the entire thickness of the cervix. The edges were approximated with interrupted sutures. The patient left the operating room in good condition.

The pathological report revealed "the presence of a thickened edematous, surface squamous epithelium, beneath which there is a dense fibrous stroma infiltrated by blood cells, lymphocytes and plasma cells. Firmly attached to this, and completely replacing the glandular structure, is a mass of organized blood clot containing necrotic decidual elements and chorionic villi. This would appear to be the point of nidation."

The patient made an uneventful recovery. On April 21, 1951, the hemoglobin was 12.3 Gm. per cent and the red blood cell count was 4.56 million. She was discharged April 24, 1951.

CASE 3.—A 36-year-old gravida iii, para ii, was admitted to the hospital May 4, 1951, with a history of dyspareunia and postcoital spotting of 2 weeks' duration. Menses had been grossly irregular for many years, averaging one period every 3 to 6 months. The last menstrual period had begun April 1, 1951. The patient suspected that she might be pregnant, as she had nausea and tender breasts. Her previous pregnancies in 1937 and 1940 had been normal.

Physical examination was negative except for the pelvis. Multiple polypoid lesions protruded from the slightly enlarged cervix. The uterus was also slightly enlarged. Urinalysis was negative. Hemoglobin determination was 10.2 grams per cent, and the erythrocyte count was 3.47 million per cubic centimeter.

On the day following admission, the polypoid lesions and the cervix were biopsied. Dilatation and curettage and conization of the cervix were performed, and all of the polypoid tissue, which was attached only to the endocervix, removed. The vagina was packed with gauze and a Foley catheter placed within the bladder.

The patient made an uneventful recovery and was dismissed from the hospital on May 8, 1951.

Tissue study revealed "markedly edematous endocervical tissue with polypoid arrangement of the cervical glands and infiltration of decidual tissue. In the conized specimen, there is decidual tissue with fibrous stroma, such as is seen in the cervical canal. There are no malignant changes."

CASE 4.—A 26-year-old housewife, gravida iii, para i, with one abortion and one tubal pregnancy, was admitted to the hospital Nov. 6, 1951, with vaginal bleeding. Her last

menstrual period had begun on Aug. 17, 1951, and she had had no complications until about 36 hours prior to admission. At this time, vaginal bleeding associated with mild abdominal cramps had begun.

The patient had had a salpingectomy for a ruptured ectopic pregnancy in 1948, and had experienced a normal pregnancy in 1950.

Physical examination was negative. The vaginal bleeding was continuous but not severe. Examination in a hospital treatment room showed a cervical body and fundus of equal size. Placental tissue was removed from the cervical os. A presumptive diagnosis of cervical pregnancy was made and the patient was prepared for operation. Urinalysis was negative. The hemoglobin was 10.5 Gm. per cent, and the erythrocyte count was 3.52 million per cubic centimeter.

At the time of the dilatation and currettage, a round mass, 5 cm. in diameter, was removed from the cervical canal. This mass consisted of placental tissue and a fetus in a sac. This tissue was firmly attached to the wall of the endocervix. Further examination revealed a constricted internal os and an endometrial cavity approximately one fourth the size of the dilated cervical canal. The entire uterus was curetted. The bleeding promptly subsided, and the patient was returned to her room in good condition.

The pathologist reported only "products of conception."

She was discharged from the hospital Nov. 8, 1951. Pelvic examination 6 weeks later was negative. In February, 1953, this patient was spontaneously delivered of a normal male infant.

CASE 5.—A 26-year-old housewife, gravida iii, para i, with one abortion, was admitted to the hospital June 18, 1953, because of vaginal bleeding of 24 hours' duration. Her last menstrual period had begun on March 17, 1953, and spotting had occurred in April and in May.

Physical examination was entirely negative. Pelvic examination in a hospital treatment room showed the fundus to be about the size of a 6 weeks' pregnancy. The cervical body was equal in size to that of the fundus, with placental tissue protruding through the os. This tissue was removed with forceps, leaving a pocket (the endocervical canal) into which three fingers could be easily inserted. A presumptive diagnosis of cervical pregnancy was made and the patient taken to the operating room.

Under anesthesia, the findings of the previous pelvic examination were confirmed. In addition, it was found that the internal cervical os was dilated less than 1 cm. in diameter. This imparted to the uterus an "hourglass" shape with the endocervical cavity being larger than the endometrial cavity. The uterine and cervical cavities were packed after curettage.

Pathological study revealed placental tissue within the endocervix and only decidual tissue within the uterine cavity.

The patient made an uneventful recovery and was discharged 2 days after operation.

Two months later, the cervix was still dilated enough to admit the index finger to a depth of 2.5 cm. Extensive endocervical cautery was done as an office procedure, and the area was observed every 3 weeks for 3 months. At the final examination, the ectocervix had a clean, healthy appearance, and the canal had diminished to less than 0.5 cm. in diameter.

The patient has subsequently had a normal pregnancy and was delivered in January, 1955. At the time of the postpartum examination, the cervix was again normal.

Comment

It is apparent from a review of the literature that there are varying degrees of "legitimacy" in a consideration of diagnostic criteria for the infrequent obstetrical entity of cervical pregnancy. The range extends from

Schneider's rigid interpretation to those of the authors who feel that no pathological proof is necessary. It has occurred to us that a classification of lower uterine segment, isthmic, and cervical implantations might proceed as follows:

I. Placental implantation in lower uterine segment ("low-lying" placenta)
II. Placenta previa
III. Corporeal and isthmicocervical implantation
IV. Isthmicocervical implantation
V. Cervical pregnancy
   A. Anatomical proof
      This category would include cases with the total uterus (hysterectomy or autopsy specimen) without previous curettement or endocervical manipulation in which total placentation was below the histological internal os. Even Schneider has stated that proper documentation of such an early case is lacking. A case such as has been photographed by Greenhill would seem to come as near to this ideal and strictest category as one could imagine.
   B. Pathological proof
      1. The products of conception should be entirely confined within and firmly attached to the endocervix. The presence of villi in endocervical stroma would be required.
      2. Decidual tissue only can be found within the endometrial cavity.
   C. Probable pathological proof
      1. Same criteria as B (above) except that the presence of villi in cervical stroma would not be required.
      2. The criteria of D (below) would be met.
   D. Clinically suggestive
      1. Uterine bleeding after amenorrhea and without cramping pain (presumptive pregnancy).
      2. A softened and disproportionally enlarged cervix equal to, or larger than, the corporeal position of the uterus. An hourglass-shaped uterus.
      3. Products of conception entirely confined within and firmly attached to the endocervix.
      4. A snug internal os.
      5. Partially open external os.

All of the above varieties are, of course, to be differentiated from cervical abortion. The criteria for the proper and precise identification of this entity have been presented.[11]

We submit our first 2 cases as instances of cervical pregnancy with probable pathological proof (V,C) and our last 3 cases as instances of cervical pregnancy which were clinically identified (V,D).

We are aware that many of the cases of cervical pregnancy reported to this date have demonstrated severe hemorrhage. It is also obvious, from careful review of this literature, that this concept may have been overpresented—not only because there are a significant number of cases that have been identified by reliable observers without massive hemorrhage but also because of the

following possibilities: (a) Schneider's commentary that much of the massive bleeding may have been associated with the cervicoisthmic varieties of placentation; (b) many cervical pregnancies "are aborted" so early that they are not identified and disruption of cervical tissue has not been profound; (c) the previous occurrence of fetal death may have permitted the development of a plane of separation by thrombosis, etc.

It is, contrariwise, obvious that with massive trophoblastic invasion of the endocervical mucosa and stroma, early termination and massive hemorrhage might well result because of the predominantly fibrous and, therefore, noncontractile nature of the human cervix.[12] Our cases had brisk but not massive bleeding. The 2 most significant symptoms are bleeding, usually becoming progressively more severe, and the absence of cramping pain.

The typical clinical finding is a uterus with the products of conception contained entirely within and attached to the endocervix. Only decidual tissue may be obtained from the endometrial cavity. This imparts to the uterus an "hourglass" shape with the cervical portion equal to, or somewhat larger than, the corporeal portion. The internal os is usually tightly closed.

Treatment of cervical pregnancy consists of adequate blood replacement, removal of the products of conception, and curettage of the endometrial cavity and endocervix. Packing of the endometrial cavity, the dilated cervical canal, and vagina (for counterpressure) may be required.

Flanagan and Walsh[8] stated that the diagnosis is rarely made before operation because of the infrequency of the condition, and because the heavy bleeding forces the physician to take the patient to the operating room as soon as possible. If the possibility of endocervical implantation is kept in mind, however, it is possible that careful preliminary pelvic examination may direct one toward the proper diagnosis. A correct presumptive diagnosis was made in 2 of our cases.

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Discussion

DR. L. M. RANDALL, Rochester, Minn.—A review of publications concerning cervical pregnancy reveals considerable quibbling in the interpretation of data presented in the case reports. Some authors hold to strict criteria requiring histologic proof while others adopt a more liberal attitude toward the authenticity of clinical observations. Examples of this diversity of approach are evident in two publications that appeared in 1957. One

author approved 17 of the cases reported in the literature as bona fide examples of cervical pregnancy while the second author was willing to accept 52 cases as representative of the entity. This variation in numbers could be accepted as a controversy between the scientific and the practical point of review.

In my opinion we may well accept the larger figure as evidence that cervical pregnancy or some variant thereof such as cervicoisthmic pregnancy, which may be as clinically important, occurs more frequently than has been presumed in the past. It would seem that the essayists support this point of view, for 3 of their 5 cases are classified as "clinically identified." This attitude should increase our index of suspicion and awareness of the condition and thus lead to earlier diagnosis and adequate treatment.

The possibility of fetal salvage is essentially nil when the fertilized ovum is primarily implanted in the cervix. Accordingly, cervical pregnancy becomes of primary importance to the mother and treatment based on the clinical findings transcends the establishment of an exact histologic diagnosis. Indeed the latter, in the final analysis, depends on examination of the unaltered extirpated uterus. As has been mentioned, there seems to be but one specimen extant where an unmolested conceptus lies attached in the endocervical canal entirely below the anatomic internal os. This is not surprising for by the time hysterectomy may be performed in these cases the cervix and site of implantation will have been considerably mutilated by other attempts at treatment.

The criteria necessary for recognition of cervical pregnancy, as stated in the presentation, seem relatively straightforward, sufficiently so that recognition should not be too difficult. Likewise the treatment is direct—evacuation and hemostasis.

The authors mention that the incidence of severe hemorrhage has been overstated in association with true cervical pregnancy and that it is more likely to occur with cervicoisthmic pregnancy. It appears that accurate clinical differentiation between the two varieties is not invariably to be depended upon and therefore facilities for immediate and adequate replacement of blood should be available before any treatment is initiated. We must be grateful to the essayists for a meticulous presentation of an important, if rare, obstetric entity.

THE ENDOMETRIUM BEFORE AND AFTER WEDGE RESECTION OF THE OVARIES IN THE STEIN-LEVENTHAL SYNDROME*

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ENDOMETRIAL carcinoma as a complication of the Stein-Leventhal syndrome has received recent attention. In 1957 Jackson and Dockerty[9] reported on a group of 44 cases of the Stein-Leventhal syndrome in which 17 women had carcinoma of the endometrium. They emphasized the association of endometrial carcinoma as a late complication of this symptom complex. Sommers and associates,[13] Dockerty and co-workers,[2] and DeVere and Dempster[1] have also called attention to this as a suspected late complication of the syndrome. Dockerty[2] has noted that approximately 20 per cent of women under 40 who developed carcinoma of the uterine fundus gave clinical evidence of the Stein-Leventhal syndrome.

Stein[17-19] on several occasions has stated that he has never encountered an instance of endometrial carcinoma in any of the patients with the Stein-Leventhal syndrome on whom wedge resection of the ovaries had been performed. He feels that proof of an etiological relationship between polycystic ovaries and carcinoma of the endometrium is lacking, and that in the cases with endometrial carcinoma or hyperplasia the ovarian pathology is not the same as in the typical Stein-Leventhal syndrome. Despite this impression, he advocates that uterine curettage be performed in all cases and, if endometrial hyperplasia is found, the patient be followed carefully for carcinoma.

A review of the literature revealed a surprising lack of specific information on the endometrial changes associated with the polycystic ovary syndrome other than the reported relationship of this symptom complex to endometrial carcinoma. Stein[17] found the endometrium to be predominently in the early or mid-proliferative phase. He observed neither atrophy nor secretory activity. On two occasions he found endometrial hyperplasia. One of these patients had received prolonged hormonal therapy. Ingersoll,[7] in a recent discussion of the syndrome, reported his findings in 19 preoperative biopsies. Seventeen revealed proliferative activity, one was atrophic, and one was hyperplastic. Jackson and Dockerty[9] found a proliferative endometrium in 11 women, atrophic changes

*Presented at the Twenty-sixth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., Oct. 2-4, 1958.

in 2, and hyperplasia in 2. Keettel and associates[10] reported 5 cases with a proliferative endometrium, 3 with atrophy, one with hyperplasia, and one with a secretory endometrium.

The lack of detailed reports of the endometrial changes seen in association with the Stein-Leventhal syndrome and the apparent discrepancies reported in the literature prompted this report. As many cases of this symptom complex as possible have been collected and followed with preoperative endometrial biopsies, bilateral wedge resection of the ovaries, and postoperative endometrial biopsies to determine (1) what type of endometrial abnormalities, if any, are present, (2) the effect of surgery on any endometrial changes which may have occurred, and (3) the possible relationship between the Stein-Leventhal syndrome and endometrial carcinoma.

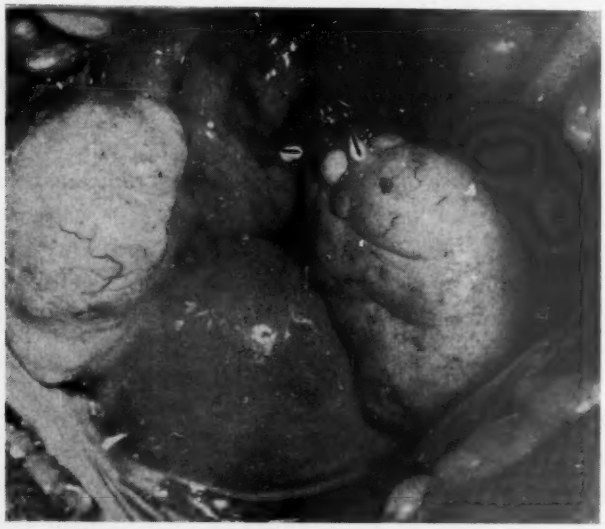


Fig. 1.—Typical large, polycystic ovaries seen in the Stein-Leventhal syndrome.

Materials and Methods

The Stein-Leventhal syndrome is characterized by menstrual irregularity, sterility, hirsutism (in about 50 per cent of the cases), occasional obesity, and, in all cases, bilateral polycystic ovaries. The urinary follicle-stimulating hormone, estrogens, and basal metabolic rate are normal.[3] 17-Ketosteroids are normal to slightly elevated.[3, 10] The ovaries are 3 to 4 times normal size, pale, slightly lobulated, and have a thick pearly white capsule covering the surface (Fig. 1). There are multiple small to moderate-sized fluid-filled cysts beneath the thick cortical rind (Fig. 2). Microscopically there is a pronounced cortical fibrosis (Fig. 3), hyperthecosis (Fig. 4), multiple follicle cysts lined by one to several layers of granulosa cells or compressed theca interna cells, and a characteristic lack of recent corpora lutea.

A total of 17 cases having the clinical picture and ovarian findings consistent with the Stein-Leventhal syndrome were available for study (Table I). An endometrial biopsy or curettage was performed in each case before ovarian resection. There was one case in which the clinical history might not be considered typical (Case 17). This patient had been delivered of a term infant 8

months prior to resection of the ovaries. The clinical picture as well as the ovarian changes she exhibited was otherwise quite characteristic. Prior to the pregnancy she had had a long history of sterility with menstruation occurring at 4 month intervals. Ingersoll[7] has commented that these patients may have an ovulatory period at rare intervals. Pregnancy is possible in the latter event.

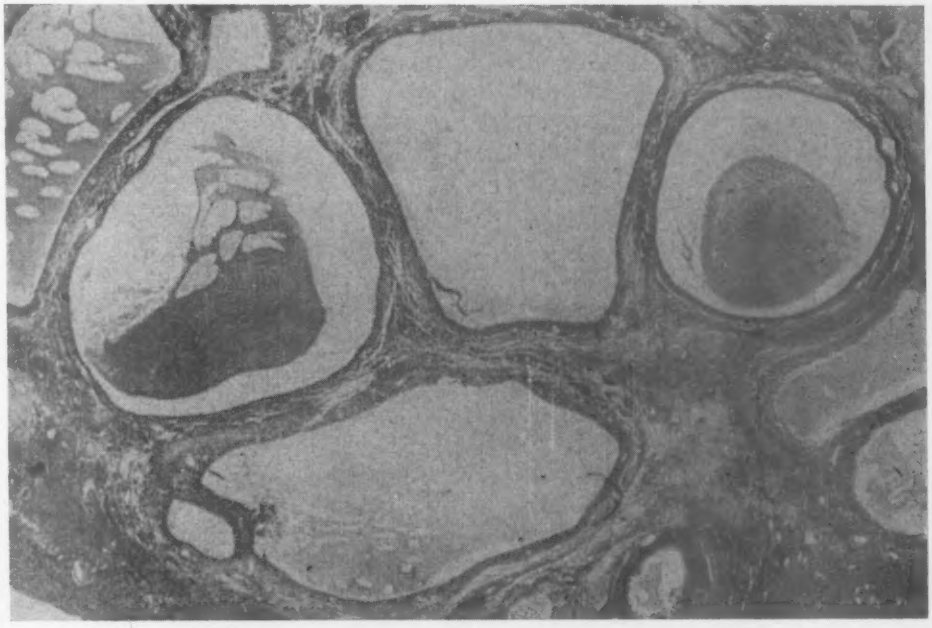


Fig. 2.—Multiple cysts noted beneath the thick cortical rind.

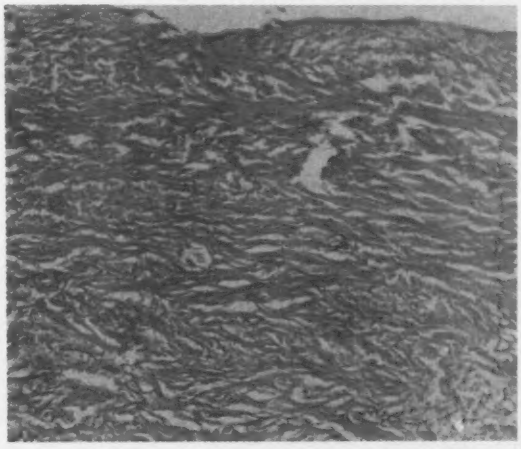


Fig. 3.—Marked cortical fibrosis seen in the ovaries of all of our patients.

One to four preoperative specimens of endometrium were available for study on each case. An attempt was made to obtain at least one postoperative endometrial biopsy, in the latter half of the menstrual cycle, from each patient. This was possible on 15 of the 17 patients studied. Repeat periodic postoperative endometrial biopsies were obtained on those who exhibited hyperplasia prior to resection of the ovaries even if a normal secretory endometrium was found on an earlier biopsy.

TABLE I. SUMMARY OF CLINICAL AND LABORATORY FINDINGS IN 17 PATIENTS WITH THE STEIN-LEVENTHAL SYNDROME

CASE	AGE	MENSTRUAL HISTORY	HIRSUTISM	STERILITY	OBESITY	POLYCYSTIC OVARIES	17-KETO-STEROIDS	FSH	ESTROGENS
1. R. H.	27	Amenorrhea followed by metrorrhagia	Yes	Yes	Moderate	Yes	Normal to slightly elevated	Normal	Normal
2. M. B.	23	Amenorrhea	Yes	Yes	No	Yes	Normal	Normal	Normal
3. L. W.	30	Menstruation every 2 to 6 months	Yes	Yes	Yes	Yes	Normal	—	—
4. C. L.	30	Oligomenorrhea	Slight	Yes	No	Yes	Normal	—	—
5. D. E.	19	Oligomenorrhea followed by menometrorrhagia	Slight	Yes	No	Yes	—	—	—
6. G. W.	24	Oligomenorrhea followed by menometrorrhagia	No	Yes	No	Yes	—	—	—
7. B. W.	28	Menometrorrhagia	No	Yes	Yes	Yes	—	—	—
8. D. S.	30	Oligomenorrhea	Yes	Yes	No	Yes	Normal	—	—
9. V. C.	32	Oligomenorrhea	Yes	Yes	Slight	Yes	Slightly elevated	—	—
10. A. T.	21	Amenorrhea followed by menometrorrhagia	Slight	Yes	No	Yes	—	—	—
11. C. B.	36	Amenorrhea followed by irregular spotting	Yes	Yes	Slight	Yes	—	—	—
12. R. M.	20	Amenorrhea	Slight	Yes	No	Yes	Normal	Normal	—
13. J. R.	23	Oligomenorrhea followed by menometrorrhagia	No	Yes	No	Yes	Normal	Normal	—
14. O. O.	28	Oligomenorrhea followed by menometrorrhagia	Yes	Yes	Yes	Yes	—	—	—
15. E. M.	26	Menometrorrhagia	No	Yes	No	Yes	—	—	—
16. M. O.	23	Amenorrhea followed by menometrorrhagia	No	Yes	No	Yes	—	—	—
17. L. L.	23	Oligomenorrhea followed by menometrorrhagia	No	Yes*	No	Yes	—	—	—

*Long history of sterility followed by a single pregnancy 8 months before ovarian resection.

Cystic hyperplasia is defined as endometrium demonstrating marked disparity in gland size and configuration with some glands being large and cystic while others in the same vicinity are small and tubular. The large glands are usually lined by a single layer of epithelium while the small ones may show stratification or pseudostratification. The nuclei are active and uniform in appearance and mitotic figures are not uncommon. The stroma is compact and abundant; the nuclei are active. Adenomatous hyperplasia demonstrates a more pronounced degree of epithelial proliferative activity. There is pseudostratification or stratification of the epithelium with occasional "out-budding" of the epithelium into the surrounding stroma. There is crowding together of gland structures with compression of the stroma giving an adenomatous pattern to the endometrium. The nuclei may be large and are uniform in size and shape.

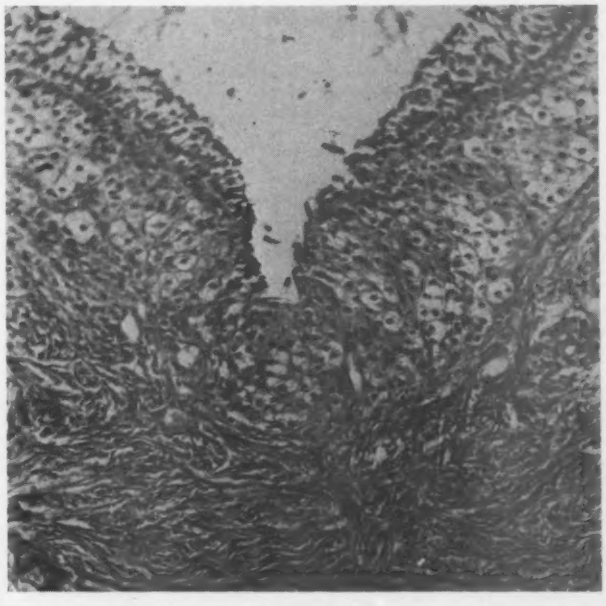


Fig. 4.—Proliferation and luteinization of the theca interna.

Cellular polarity is maintained. Atypical endometrial hyperplasia is characterized by the above changes with intraluminal tufting or papillary projections, cellular and nuclear atypism, and slight loss of cellular polarity which is not as pronounced as in adenocarcinoma.

Results

The results are summarized in Tables II and III. Endometrial tissue was available from 17 patients prior to wedge resection of the ovaries. Three showed atrophic change, 4 were in the early to mid-proliferative phase, 4 revealed a cystic hyperplasia, 3 demonstrated adenomatous hyperplasia, and in 3 patients the endometrium was interpreted as atypical hyperplasia.

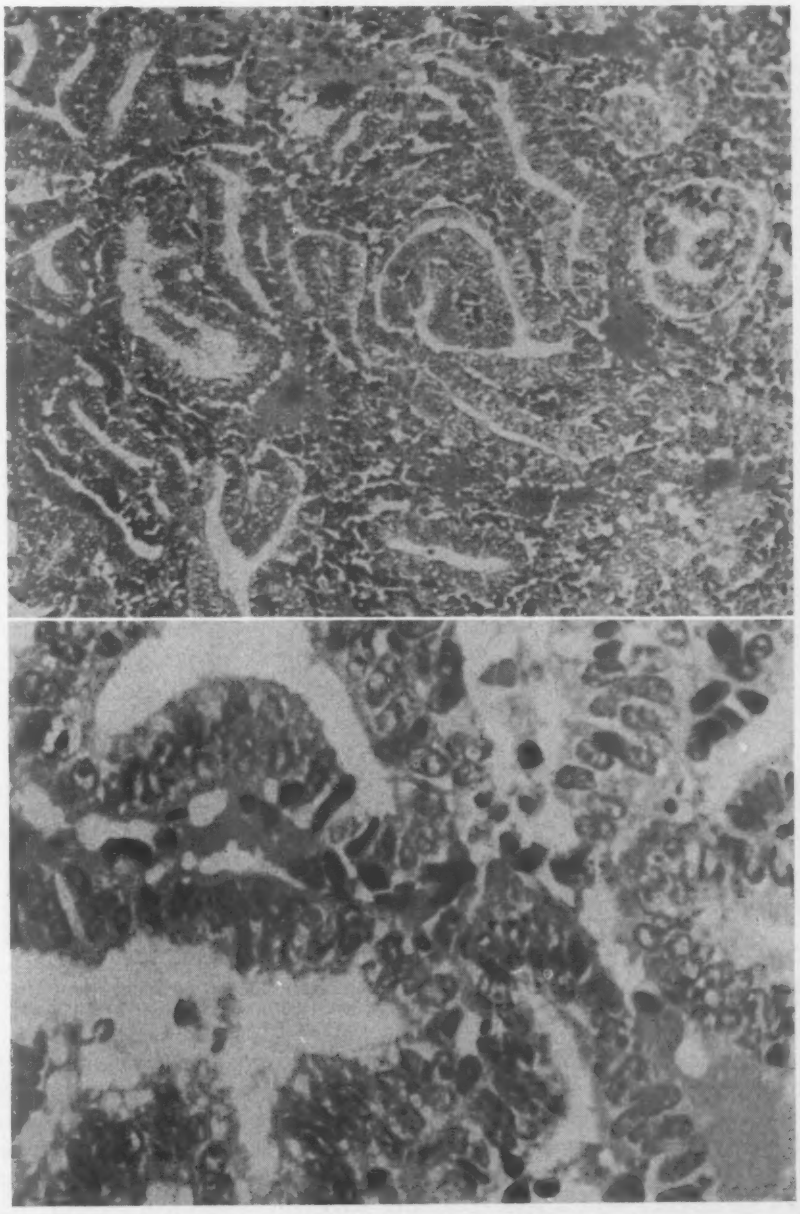
In the group with atypical hyperplasia, one patient (Case 1, Table II) had several endometrial biopsies and curettages over a 2 year period prior to resection of the ovaries. The first specimen demonstrated mild adenomatous hyperplasia. The one obtained just prior to resection of the ovaries revealed a marked degree of atypical hyperplasia (Fig. 5, *A* and *B*). This was not considered to be carcinoma on the basis of the relative degree of nuclear uniformity and the over-all maintenance of cellular polarity. The ovarian resection done

TABLE II. ENDOMETRIAL AND OVARIAN PATHOLOGY AND CLINICAL RESULTS IN 17 PATIENTS WITH THE STEIN-LEVENTHAL SYNDROME

CASE	AGE	PREOPERATIVE ENDOMETRIUM	OVARIES	POSTOPERATIVE ENDOMETRIUM	RESULTS
1. R. H.	27	1. Hyperplasia, adenomatous 2. Hyperplasia, adenomatous, mild 3. Atypical hyperplasia	Cortical fibrosis Hyperthecosis Multiple cysts	Hyperplasia, adenomatous	2 normal periods then menometrorrhagia
		Hyperplasia, adenomatous	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
2. M. B.	23	Proliferative	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
3. L. W.	30	Hyperplasia, adenomatous	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
4. C. L.	30	Atrophy	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
5. O. E.	19	Atrophy	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
6. G. W.	23	Hyperplasia, adenomatous	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
7. B. W.	28	Hyperplasia, cystic	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
8. D. S.	30	Proliferative	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
9. V. C.	32	1. Hyperplasia, cystic 2. Atypical hyperplasia	Cortical fibrosis Hyperthecosis Multiple cysts	Proliferative	Regular periods
10. A. T.	21	1. Proliferative 2. Proliferative	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods
11. C. B.	36	Atypical hyperplasia	Cortical fibrosis Hyperthecosis Multiple cysts	1. Atypical hyperplasia 2. Secretory with focal atypical hyperplasia 3. Atypical hyperplasia	Irregular periods Regular periods
12. R. M.	20	Atrophy	Cortical fibrosis Hyperthecosis Multiple cysts	Proliferative (before patient began to menstruate)	Regular periods
13. J. R.	23	Proliferative	Cortical fibrosis Hyperthecosis Multiple cysts	——	Regular periods
14. O. O.	28	Hyperplasia, adenomatous	Cortical fibrosis Hyperthecosis Multiple cysts	——	Regular periods
15. E. M.	26	Hyperplasia, cystic	Cortical fibrosis Hyperthecosis Multiple cysts	Proliferative with focal cystic hyperplasia	Irregular periods
16. M. O.	23	Hyperplasia, cystic	Cortical fibrosis Hyperthecosis Multiple cysts	1. Atypical hyperplasia 2. Hyperplasia, cystic	Amenorrhea
17. L. L.	23	Hyperplasia, cystic	Cortical fibrosis Hyperthecosis Multiple cysts	Secretory	Regular periods

following this curettage was performed via a posterior colpotomy and the resection of the left ovary was not adequate. Subsequently she had 2 normal periods followed by amenorrhea and menometrorrhagia. Repeat curettage 3 months later showed focal areas of adenomatous hyperplasia and a biopsy 6 months after operation revealed marked adenomatous hyperplasia (Fig. 6). Reoperation was felt to be indicated because of the prior inadequate resection of the left ovary. Laparotomy revealed both ovaries to be enlarged and cystic and about 50 per cent of each was removed. The patient was amenorrheic for

A.



B.

Fig. 5.—*A*, Case 1. Atypical hyperplasia. Preoperative biopsy. (Hematoxylin and eosin. ×100; reduced ¼.) *B*, Case 1. Atypical hyperplasia. The nuclei are relatively uniform and cellular polarity is maintained. (Hematoxylin and eosin. ×400; reduced ¼.)

3 months following which she began to have cyclic menstrual periods. Two endometrial biopsies obtained within 10 days of the onset of menstruation revealed secretory activity (Fig. 7).

Fig. 6.—Case 1. Adenomatous hyperplasia. Biopsy obtained 6 months after ovarian resection. (Hematoxylin and eosin. ×100; reduced ⅓.)

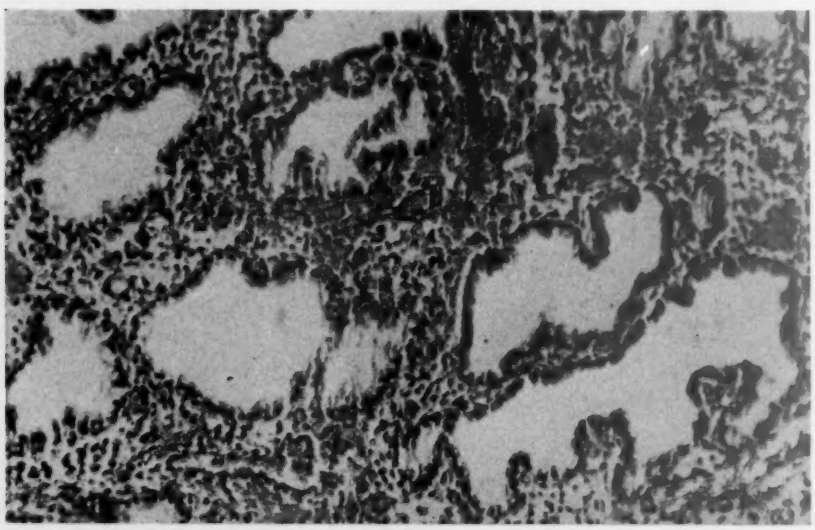


Fig. 7.—Case 1. Secretory activity. Biopsy obtained after second ovarian resection. Periods now normal and regular. (Hematoxylin and eosin. ×100; reduced ¼.)

The second woman (Case 11) demonstrating atypical hyperplasia prior to treatment (Fig. 8) again revealed atypical hyperplasia 4½ months postoperatively (Fig. 9). An endometrial biopsy 6 months postoperatively showed well-developed secretory activity (Fig. 10, *A*) with a focal area of atypical hyperplasia (Fig. 10, *B*). Eight months after operation biopsy demonstrated atypical hyperplasia (Fig. 11) and a hysterectomy was recommended. Prior to the first postoperative biopsy the patient experienced 2 episodes of heavy vaginal bleeding occurring at 2 month intervals. Subsequent to this the periods have occurred regularly every 40 days.

TABLE III. SUMMARY OF ENDOMETRIAL FINDINGS IN 17 PATIENTS WITH THE STEIN-LEVENTHAL SYNDROME

PREOPERATIVE BIOPSY		POSTOPERATIVE BIOPSY			
		SECRETORY	PROLIFERATIVE	SWISS-CHEESE HYPERPLASIA	ATYPICAL HYPERPLASIA
Atypical hyperplasia	3	1	1		1
Adenomatous hyperplasia	3	2			
Cystic hyperplasia	4	2		2	
Proliferative	4	3			
Atrophy	3	2	1		
Total	17	10	2	2	1

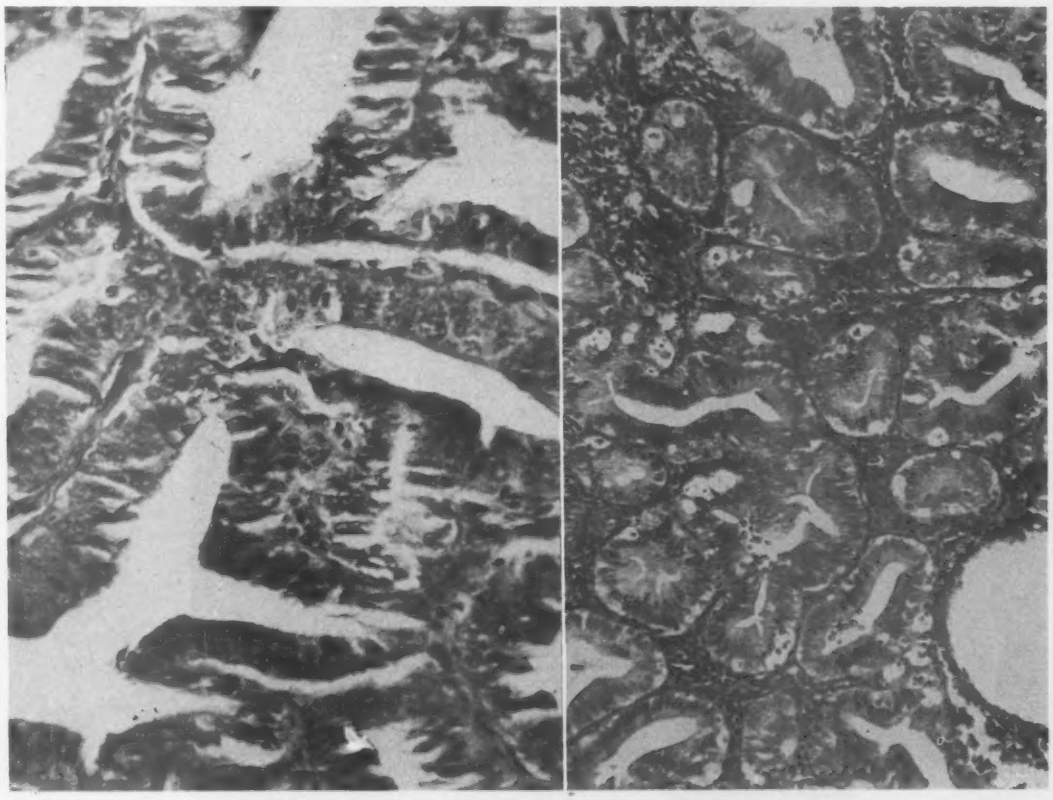


Fig. 8. Fig. 9.

Fig. 8.—Case 11. Atypical hyperplasia. Preoperative specimen. (Hematoxylin and eosin. ×200; reduced ¼.)

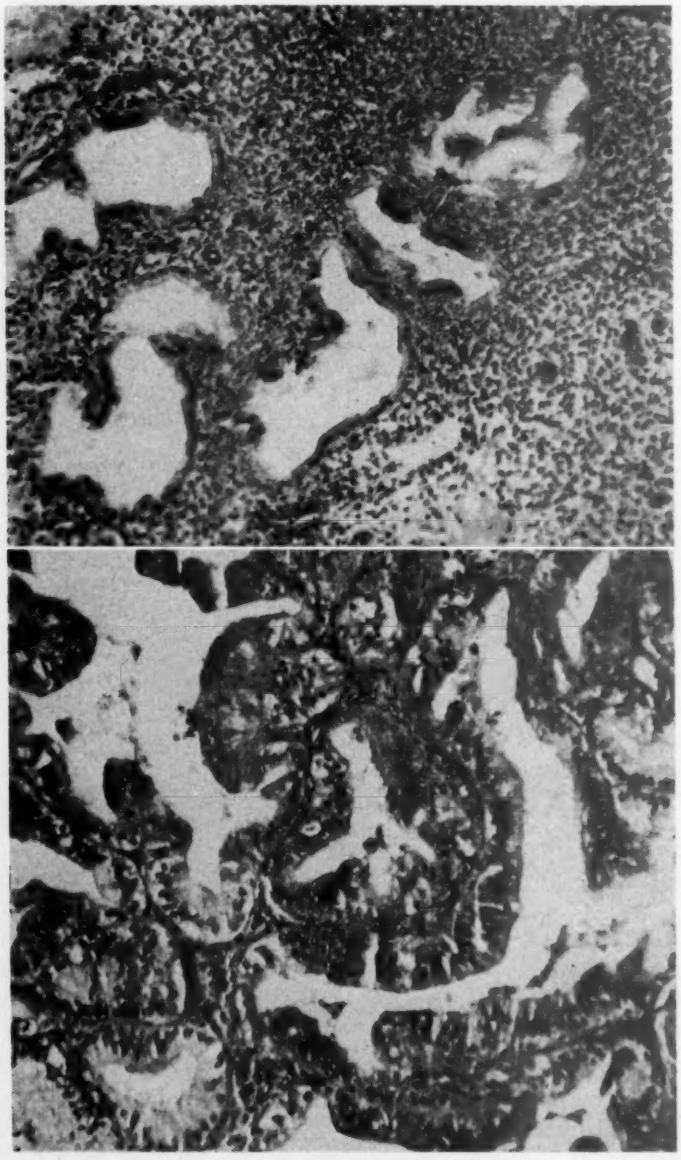
Fig. 9.—Case 11. Atypical hyperplasia again demonstrated 4½ months after wedge resection of ovaries. Periods heavy and irregular. (Hematoxylin and eosin. ×100; reduced ¼.)

The third patient (Case 9) demonstrating atypical hyperplasia (Fig. 12) had an excellent clinical response with cyclic periods occurring every 28 days after operation. An endometrial biopsy taken several months after surgery on the twentieth day of the cycle revealed a proliferative endometrium. This would infer that she had not ovulated that month. No evidence of the atypism noted before operation was seen.

There were 3 women with a preoperative diagnosis of adenomatous hyperplasia. Following operation, endometrial biopsies on 2 demonstrated a secretory endometrium. A follow-up biopsy was not obtained on one. All 3 women have been having regular menstrual periods.

Four patients had cystic hyperplasia preoperatively (Fig. 13). This lesion persisted after ovarian resection in 2. One has been amenorrheic since operation, and the other has had irregular periods for the 9 months that she has been followed. Biopsies from the other 2 women revealed a secretory endometrium. Their clinical response has been good.

A.



B.

Fig. 10.—*A*, Case 11. Six months after operation. Secretory activity. (Hematoxylin and eosin. ×100; reduced ¼.) *B*, Case 11. A focal area of atypical hyperplasia noted in an otherwise normal secretory endometrium. Menstruating every 40 days in normal amount. (Hematoxylin and eosin. ×100; reduced ¼.)

Four patients had a preoperative proliferative endometrium. Three subsequently were found to have a well-developed progestational endometrium, and one patient was lost to follow-up. All had excellent clinical responses.

Three women had an atrophic endometrium prior to operation. All 3 resumed normal menstrual function postoperatively. Two have demonstrated a secretory endometrium on subsequent biopsies. A biopsy obtained on the third patient 6 weeks after operation, several weeks before she began to menstruate, showed early proliferative activity.

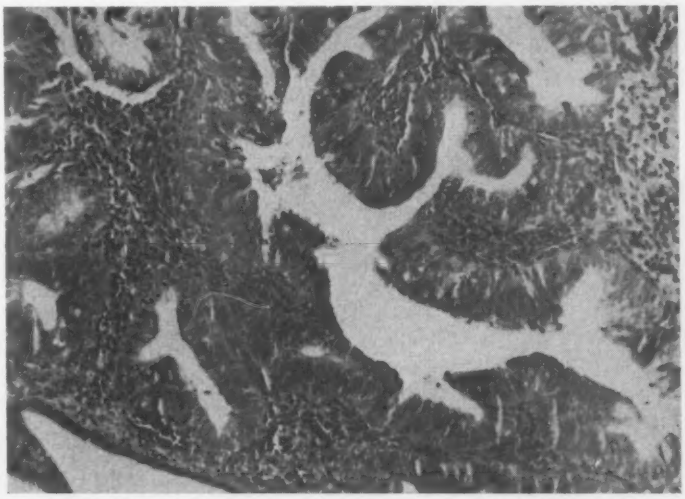


Fig. 11.—Case 11. Eight months after operation. Atypical hyperplasia again demonstrated. (Hematoxylin and eosin. ×100; reduced ⅓.)

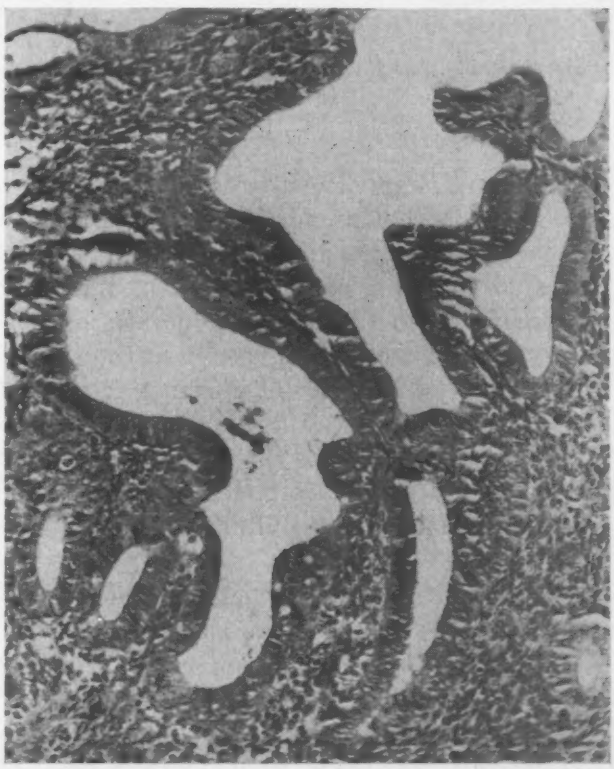


Fig. 12.—Case 9. Atypical hyperplasia. Preoperative specimen. (Hematoxylin and eosin. ×100; reduced ⅓.)

Comment

This series of 17 cases is too small for definite conclusions because the careful selectivity used made available for study only a limited number of patients with the Stein-Leventhal syndrome. The clinical picture and ovarian changes in our patients were compatible with this symptom complex. The clinical response—resumption of normal menstrual function in 15 of the 17 patients (88 per cent)—falls close to the 95 per cent return of cyclic menses reported by Stein.[17, 18] The large majority have not been followed long enough to evaluate the conception rate.

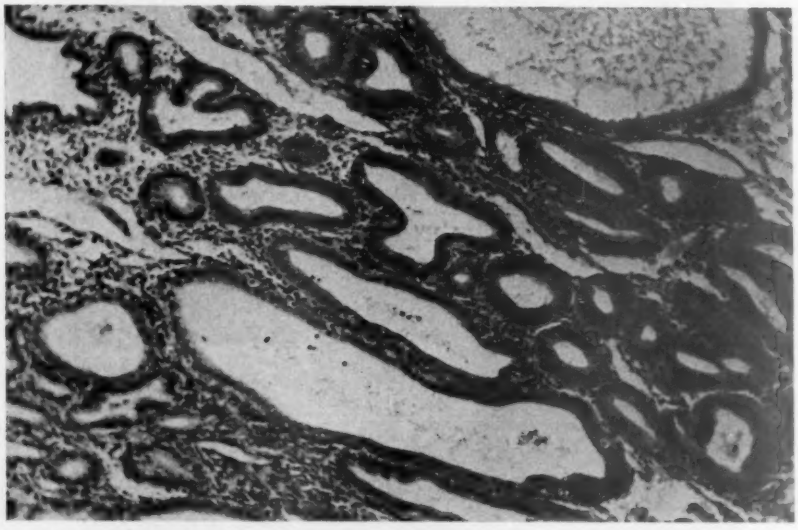


Fig. 13.—Case 16. Cystic hyperplasia. Preoperative specimen. (Hematoxylin and eosin. ×100; reduced ¼.)

Six of the 10 patients who demonstrated endometrial hyperplasia preoperatively revealed no evidence of this lesion following ovarian resection. The 3 with atypical hyperplasia before treatment are of interest. Endometrial atypism has disappeared following operation in 2 of these women. The third patient, after evidence of return of ovulatory periods on one occasion, again demonstrated the atypical endometrial hyperplasia noted before ovarian resection. She is 36 years of age and may fit into that group of patients who did not receive treatment early enough and whose endometrial changes are no longer reversible. This case emphasizes the need for early treatment of these patients as well as the necessity for careful follow-up when endometrial hyperplasia is found, despite the fact that the clinical response to treatment may be good.

Jackson and Dockerty[9] reported the high incidence of endometrial carcinoma in untreated cases of the Stein-Leventhal syndrome. They regard carcinoma as a late complication. The 27 patients in their study who did not have endometrial carcinoma had either wedge resection of the ovaries performed or bilateral oophorectomy. Those with carcinoma did not have ovarian resection and were several years older than those without carcinoma. The women whom Stein[17, 18] has followed, who had a wedge resection of the ovaries, have had no

recurrences of symptoms and none have developed carcinoma. Resection of the ovaries had also not been performed in the cases of endometrial carcinoma in young women with a clinical picture compatible with the Stein-Leventhal syndrome reported by Dockerty and associates,[2] Sommers and co-workers,[13] and Speert.[15] The findings discussed above would suggest that in women with the Stein-Leventhal syndrome it is the untreated patient who may eventually develop carcinoma, but early wedge resection of the ovaries may interrupt this process of endometrial change and prevent the development of malignancy.

Considerable evidence has been accumulated linking prolonged, unopposed estrogen stimulation of the endometrium to endometrial hyperplasia and carcinoma.[2, 4, 5, 11, 12, 14, 16] Jackson and Dockerty[9] as well as Sommers and Wadman[14] have expressed the feeling that in the Stein-Leventhal syndrome the patients may be receiving a prolonged, though not necessarily elevated, estrogenic stimulation to the endometrium. This stimulation is not interrupted by the release of progesterone after ovulation. Gusberg[4] found the response to estrogen in the form of endometrial hyperplasia to be related to the persistent stimulus rather than to the quantity of estrogen. Speert[15] suggested that women who develop endometrial carcinoma in the first 4 decades of life conform in general to a specific hormonal pattern characterized by a prolonged, continued, and unopposed estrogenic activity. Evidence of ovulation in this group of women was rare. Wall[21] has reported 2 cases of pituitary adenoma associated with endometrial carcinoma. He emphasized the frequent occurrence of various endocrinopathies with endometrial malignancy. Most of the available data suggest there is no elevation of estrogen in patients with the Stein-Leventhal syndrome[3, 10]; however, the failure of ovulation may allow a prolonged and unopposed action of estrogen on the endometrium at either normal or subnormal levels.

Gusberg[4] called attention to a pattern of adenomatous hyperplasia which he believes bears a constant relationship to estrogen stimulation in both benign and malignant disease. He felt that he could observe a progression from adenomatous hyperplasia to malignancy. Hertig and Sommers[6] indicated that cystic hyperplasia is a frequent, important, and remote forerunner of carcinoma, but that adenomatous hyperplasia appears to be a more immediate precursor of endometrial carcinoma. They stressed, however, that none of the endometrial changes, such as adenomatous or cystic hyperplasia, anaplasia, etc., is considered evidence of irreversible neoplasia. Cases have been encountered in which hyperplasia and anaplasia were replaced by a normal endometrium following establishment of ovulation in premenopausal patients.

The above as well as other[16, 20] material suggests that endometrial carcinoma may be preceded for years by various degrees of hyperplasia, and that the latter and even possibly the former may be related to unopposed estrogen stimulation. Interruption of this stimulation and resumption of normal ovulation may halt the progression to endometrial hyperplasia and malignancy. Sommers and Wadman[14] have also emphasized this point. Wedge resection of the ovary in the Stein-Leventhal syndrome may accomplish this as was demonstrated in 6 of our 10 patients who had hyperplasia before operation.

Many of the carcinomas reported in association with the Stein-Leventhal syndrome were of a low grade of malignancy with very few recurrences noted after treatment. Novak and Rutledge[12] reported on a group of women with atypical endometrial hyperplasia simulating adenocarcinoma. The follow-up on most of these women confirmed the opinion that the patients did not have malignancy. It is suggested that some of the reported cases of endometrial carcinoma associated with the Stein-Leventhal syndrome may be demonstrating severe degrees of atypical hyperplasia rather than carcinoma. If this is the case, early resection of the ovaries may be followed by a return of the endometrium to normal.

Conclusions

The findings presented indicate that varying degrees of endometrial change may be seen in association with the Stein-Leventhal syndrome. The changes characterized by hyperplasia may be an individual biological response of the patient to prolonged, unopposed estrogen stimulation of the endometrium since these patients rarely ovulate.

Wedge resection of the ovaries will bring about a reversion of the endometrium to a normal pattern in most instances.

Development of endometrial carcinoma in most of these patients can probably be prevented by adequate resection of the ovaries.

A diagnostic curettage should be done on all women with the clinical characteristics of the Stein-Leventhal syndrome before treatment.

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Discussion

DR. W. C. KEETTEL, Iowa City, Iowa.—The essayist has presented three aspects of the polycystic ovary syndrome: (1) pretreatment endometrial histology; (2) posttreatment changes; and (3) the possible relationship to endometrial carcinoma.

Since the clinical menstrual history varies from menometrorrhagia to infrequent periods and amenorrhea, it is not surprising to find a variety of endometrial patterns. In our group of 24 patients with diagnoses of the Stein-Leventhal syndrome, the preoperative endometrial biopsies showed the following distribution: In 6 patients no material was available; 8 patients had a proliferative endometrium; 5 endometria were atrophic with evidence of estrogen deficiency; 3 were hyperplastic; and 2 showed atypical secretory changes. There was no evidence of premalignant endometrial hyperplasia such as the authors have described.

Postoperatively all but 2 individuals have menstruated regularly and the majority have shown evidence of consistent ovulation. Eight of the 19 patients followed a sufficient time have become pregnant. The 3 patients with endometrial hyperplasia have reverted back to a normal endometrial pattern.

The authors mentioned that amenorrhea after a pregnancy episode was not typical and perhaps these patients should be eliminated. We feel this is not uncommon. Five of our patients were seen, 3 to 5 years after a delivery, with persistent amenorrhea. Preceding the pregnancy the periods had been irregular. It is interesting that none of the authors' patients have become pregnant even though some have been followed from 12 to 18 months. They mentioned that some were single. Is it wise to treat a single person by surgery just to improve the regularity of menstruation? Should not the surgery be postponed until after marriage and then done for the correction of her infertility? It has been our impression that conception is most likely to occur in the first few months following surgery.

In 1957 Jackson and Dockerty compared the clinical history and ovarian changes of 27 patients having the Stein-Leventhal syndrome with those of 16 patients under the age of 40 who had endometrial carcinoma associated with polycystic ovaries. It was noted that many features such as physical characteristics and menstrual histories were similar. It was their conclusion that certain patients with the Stein-Leventhal syndrome may develop endometrial cancer because of the similarity of these two groups. This is not convincing since none of their known Stein-Leventhal patients have developed endometrial carcioma. With our present knowledge it is difficult to define this syndrome accurately. Should it be on the basis of clinical history and findings, ovarian histology, gross ovarian appearance, hormonal findings, or the ovarian response to FSH? At the present time no doubt several different entities are so classified.

Sommers has reported 740 unselected autopsies on females in which he found bilateral polycystic ovaries in 3.5 per cent. In this group with the polycystic ovaries there was a significant increase in the number of the granulated basophils, indicating altered function of the pituitary. Polycystic ovaries have been reported in other situations where there seems to be pituitary overactivity such as in the newborn of diabetic mothers, children with precocious puberty, adults with acromegaly, and young women with breast carcinoma.

Bradbury and I in our laboratory and Ingersoll and McArthur from Boston have demonstrated rather consistent LH excretion in patients with this syndrome. We have also noted that the polycystic ovary is unusually sensitive to FSH (sheep pituitary) stimulation, while control patients have not shown a similar response. These findings suggest a rather constant excessive luteinizing hormone stimulation in the polycystic ovary syndrome.

While there is increasing evidence that endometrial carcinoma may be preceded by a precancerous stage, this is not yet established. The cause of these endometrial changes is likewise not clearly understood, but it is possible that hormonal aberrations may be of etiological significance. However, is one justified to conclude that since certain women with endometrial cancer have polycystic ovaries, these women must have had an unrecognized Stein-Leventhal syndrome for years preceding the endometrial carcinoma? Perhaps the abnormal hormonal changes influenced the endometrium and ovaries simultaneously. It would seem unwise at the present time to assume that the Stein-Leventhal syndrome is a precursor of endometrial cancer and advocate wedge resection as prophylaxis.

CHLOROTHIAZIDE THERAPY IN OBSTETRICS AND GYNECOLOGY*

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THREE major pharmacologic actions have been attributed to chlorothiazide (Diuril)†: diuretic, "saluretic," and hypotensive. Although in vitro chlorothiazide is a highly active carbonic anhydrase inhibitor, its pharmacologic urinary excretion profile differs from that effected by acetazolamide (Diamox) and mercurial diuretics. The augmentation of water excretion resulting from its action is similar to that of acetazolamide,[1, 2] although the effects of the drugs differ in promptness of action and in the quantitative and qualitative excretion of electrolytes.

According to Bayliss and associates[3] chlorothiazide causes an almost equimolar excretion of sodium and chloride ions. This balanced elimination of salt has been called a saluretic action. The potassium excretion is about half that of sodium; the bicarbonate excretion is about one fourth that of chloride, and the ammonia excretion occurs late, tending to protect against excessive loss of sodium and bicarbonate buffer.

In contrast, acetazolamide causes an almost equal excretion of sodium, potassium, and bicarbonate. Ammonia excretion is seldom altered. Chloride excretion occurs after the period of greatest bicarbonate loss. The disproportionate loss of sodium and potassium over chloride may be undesirable and prolonged use of the drug may cause metabolic acidosis.

The difference in rapidity of onset of action favors chlorothiazide with which effects occur within 2 hours and last for 12; with acetazolamide the initial action occurs within 6 hours and lasts from 6 to 12 hours.

Although the precise mechanism of action of carbonic anhydrase inhibitors is not entirely understood, it is believed that the enzymatic action of carbonic anhydrase in the renal tubules is inhibited, whereby the ion substitution of hydrogen for sodium is prevented. According to Gilman[4] the three important renal mechanisms for maintaining homeostasis of extracellular bicarbonate are the reabsorption of bicarbonate, the acidification of urinary buffers, and the exchange of urinary sodium with ammonium. These functions are

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†Merck & Co., Inc.

indirectly dependent upon carbonic anhydrase. Water diuresis occurs because of inhibition of renal tubular absorption of electrolytes, particularly sodium, chloride, potassium, and bicarbonate.[5]

The initial purpose of this study was to appraise the results of the administration of chlorothiazide to 50 gynecologic and 44 obstetric patients. In the gynecologic group premenstrual tension was the indication for treatment; in the obstetric group, toxemia. Early in the course of study elevated blood uric acid levels were observed in some patients. The secondary purpose of the study was to investigate the validity of this finding and to determine its relationship to chlorothiazide therapy.

Gynecologic Patients

Premenstrual tension characterized by edema, headache, mood changes, breast engorgement, bloating, and, in some patients, dysmenorrhea is presumed to be the result of salt and water retention[6] secondary to physiologic alteration in steroid metabolism.

On this basis dehydration has become established as time-honored therapy. The potent diuretic and saluretic activities of chlorothiazide appeared to make this drug ideally suited for the treatment of this syndrome. In the early part of the investigation the dose of chlorothiazide was 250 mg. given twice daily. This proved to be insufficient and a schedule of 500 mg., twice daily, was adopted. It was found propitious to give the second dose no later than 2:00 P.M. if bothersome nocturnal diuresis was to be avoided.

Because of the unprecise nature of premenstrual tension, evaluation of the results of therapy must be based upon subjective evidence. Of the 50 patients treated, over 60 per cent stated that they were substantially improved. Other forms of dehydration therapy such as salt restriction, acetazolamide, and ammonium chloride previously had been employed in 25 per cent of the patients. Several expressed preference for chlorothiazide. Improvement in mood was particularly appreciated and, in many patients, their atrabilious attitudes appeared to be mitigated. Painful breast engorgement, when a part of the premenstrual tension, was relieved in over 80 per cent. One patient, aged 36, who had endometriosis of the pelvis, lost 7 pounds in the 5 days before menstruation while taking chlorothiazide, 500 mg., twice daily. While she reported relief from premenstrual edema, headache, and nervous tension, the pelvic pain and rectal pressure from endometriosis were not alleviated.

Obstetric Patients

The usual standards for the diagnosis of toxemia (excessive weight gain, edema, hypertension, and albuminuria) were used, and 44 toxemic patients were treated with chlorothiazide. One patient had eclampsia. Of the 43 cases of pre-eclampsia, 7 were considered severe.

Therapy for mild pre-eclampsia was initiated in the outpatient department for 43 patients. Eight patients failed to show adequate improvement, and they were admitted to the hospital for more intensive treatment.

Pre-eclampsia, Mild.—The treatment of ambulatory outpatients consisted of restriction of physical activity, limitation of ingestion of salt, mild sedation, and chlorothiazide, 500 mg., given twice daily. Thirty-five patients responded favorably: the blood pressure was lowered, edema was decreased,

and weight was reduced. Seven patients, classified as having mild pre-eclampsia, had albuminuria. The maximum duration of continuous chlorothiazide therapy was 11 days although intermittent therapy was continued for longer periods. No clinical evidence of electrolyte imbalance was observed.

Pre-eclampsia, Severe.—Because 8 patients failed to respond to the program for mild pre-eclampsia, they were admitted to the hospital for more intensive management. Inpatient treatment included bed rest, mild sedation, a 1.5 Gm. sodium diet, and limitation of fluid intake to 1,200 c.c. daily. Chlorothiazide was administered in doses of 500 mg. twice daily. Fluid intake, fluid output, daily weight, and albuminuria were recorded. The laboratory studies included the determination of: hemoglobin, leukocyte count, and blood uric acid. In selected patients additional laboratory procedures included determinations of: nonprotein nitrogen, hematocrit, fibrinogen, serum sodium, potassium, chlorides, and carbon dioxide combining power.

Response to Treatment.—

Weight loss: Prompt diuresis and disappearance of dependent edema were evident in all patients (Fig. 1). The most weight lost in the first 48 hours after admission to the hospital by any one patient was 17 pounds. The average weight loss in the first 48 hours was 8.4 pounds. The change depicted in Fig. 1 is characteristic of the weight loss in response to chlorothiazide.

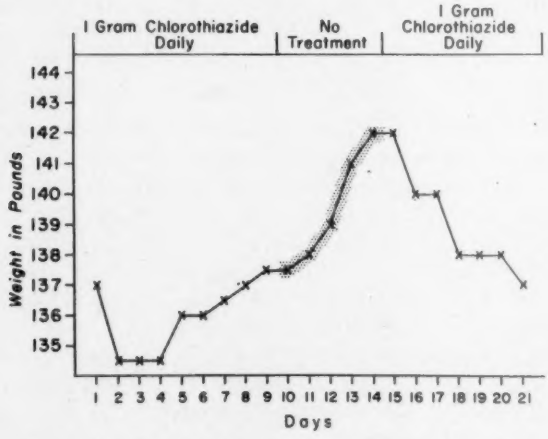

Fig. 1.—Characteristic weight loss in response to chlorothiazide.

Blood pressure: The initial blood pressures recorded for the 8 patients admitted to the hospital were: 170/114, 170/100, 160/100, 164/110, 170/88, 150/100, 178/116, and 172/110. After 48 hours of hospital treatment, blood pressure readings were recorded as follows: 150/88, 144/80, 155/110, 122/74, 144/98, 125/70, 150/70, and 160/100, respectively. Only one patient was delivered within the first 48 hours. In patients with toxemia, Chesley[7] showed that the benefits from bed rest were both diuresis and a lowering of the blood pressure. The blood pressure response in the patients treated with chlorothiazide herein observed was much the same as could be expected from bed rest alone.

Albuminuria: All patients requiring admission to the hospital because of severe pre-eclampsia had albuminuria. With hospital treatment albuminuria was decreased but it persisted to some degree in all patients with severe pre-eclampsia until after delivery. Except for blood uric acid values, all other laboratory studies were reported to be within the normal range.

That chlorothiazide was not entirely effective in the treatment of toxemia is illustrated by the case reports of the following 2 patients:

CASE NO. 1.—A 37-year-old gravida ii, para i, whose estimated date of confinement was March 2, 1958, was treated with acetazolamide and later chlorothiazide because of a gain of 5 pounds in 2 weeks, dependent edema, and elevation in blood pressure which ranged from 140/80 to 158/90. When admitted to the hospital because of false labor at 36 weeks' gestation, she weighed 162 pounds and the blood pressure was 158/90.

Chlorothiazide was administered, 500 mg., twice daily. When discharged 3 days later, she weighed 154 pounds and the blood pressure was 135/85. One week later it was necessary to discontinue chlorothiazide because of the development of a generalized maculopapular rash. Upon readmission to the hospital she weighed 160 pounds, the blood pressure was 132/90, and the urine tested 3 plus for albumin. Labor began spontaneously at 38 weeks' gestation. The duration of the first stage of labor was 15 hours. During the second stage of labor the patient had one severe eclamptic convulsion. This occurred about 17 hours after the last dose of chlorothiazide. The total number of days chlorothiazide was given was 21.

CASE NO. 2.—M. M., aged 25, primigravida, in the third trimester developed rapid weight gain and hypertension. Chlorothiazide therapy was initiated in the outpatient service. When she was 39 weeks pregnant the blood pressure was 170/106 and the urine tested 3 plus for albumin. The onset of labor at 40 weeks was spontaneous and delivery of a 7.5 pound normal female infant occurred after 5 hours of labor. After delivery, blood pressure was recorded as 140/80 and the urine tested 2 plus for albumin. Chlorothiazide, 1,000 mg. daily, was continued for 4 additional days post partum when the blood pressure was recorded at 120/72 and the urine tested negative for albumin. The total number of days chlorothiazide was administered was 15.

Experience with these patients suggested that chlorothiazide had little influence upon albuminuria and only a mild effect on hypertension. Chlorothiazide did not prevent the development of eclamptic convulsion.

Toxicity.—Side-effects related to chlorothiazide therapy were observed in 8 patients. Two complained of numbness and tingling of the fingers; 4 complained of nausea without vomiting, and 2 developed a severe generalized maculopapular rash. Administration of the drug was stopped and in each instance the complication was relieved. Dizziness and weakness occasionally attributed to chlorothiazide administration were observed to cease even with continuation of the treatment.

Hyperuricemia

Early in the present study elevations of blood uric acid levels were observed in patients receiving chlorothiazide. Previously, Laragh[8, 9] reported similar results in 6 of 7 patients under treatment. He observed that the state of hyperuricemia was asymptomatic, and that it was quickly dissipated upon discontinuation of the drug. Because urea levels of the serum were not elevated, he was of the opinion that the cause was not dehydration.

In the Henry Ford Hospital Laboratory, Division of Biochemistry, serum uric acid values are determined by the Wolfson modification of the chemical method of Benedict and Frank. The range for normal for pregnancy and nonpregnancy is between 3.0 and 5.5 mg. per 100 ml. serum and the test is probably accurate within 0.3 mg.

To test the validity of the observation that chlorothiazide causes hyperuricemia, a clinical program was designed to provide substantiating data. In addition, corollary studies were selected to test the importance of hemoconcentration and dehydration as etiological factors.

Seventeen normal obstetric patients served as subjects. Because their usual stay in the hospital was 6 days, blood samples were procured on the first and fifth postpartum days for quantitative determination of serum uric acid. In addition, in many patients hemoglobin and/or hematocrit values were determined.

The patients were divided into two groups. Group I was made up of 7 patients, the study of whom served to provide information of the alterations expected to occur from physiologic changes incident to the normal puerperium. Group II was comprised of 17 patients who received 500 mg. of chlorothiazide twice daily from the first to the sixth postpartum day.

Results

Group I, Normal Obstetric Patients Given No Chlorothiazide (Table I).—In these 7 patients the average value for uric acid on the first postpartum day was 4.9 mg. per 100 c.c. of serum and on the fifth day, 4.6 mg. This value represented a 6 per cent decrease for uric acid, a change of no statistical significance.

TABLE I. SERUM URIC ACID IN THE NORMAL PUERPERIUM

PATIENT NO.	FIRST POSTPARTUM DAY (MG. PER 100 C.C.)	FIFTH POSTPARTUM DAY (MG. PER 100 C.C.)
1	5.0	4.4
2	4.6	4.2
3	4.5	4.2
4	5.4	4.0
5	4.8	5.4
6	5.0	4.5
7	4.8	5.4
Average	4.9	4.6
Percentage change:	6 per cent decrease	

Group II, Normal Obstetric Patients Given Chlorothiazide (Table II).—The effects of the administration of chlorothiazide were observed in 17 patients. The average blood uric acid value on the first postpartum day before administration of the drug was instituted was 4.3 mg. per 100 c.c. of serum. On the fifth day, the level had increased to 5.8 mg. This represented an increase in average value of 1.5 mg., or 35 per cent. Comparative hemoglobin values were observed in 4 patients. The average values rose from 11.3 Gm. to 11.8 Gm., an increase of 4 per cent. The hematocrit in 11 patients rose in average value from 42.6 to 45.5 mm. a difference of 2.9 mm., or 7 per cent. These data are evidence that chlorothiazide is a hyperuricemic agent and that such rises in hemoglobin and hematocrit values probably do not result from hemoconcentration from dehydration.

Pre-eclampsia.—While the cause of hyperuricemia in toxemia of pregnancy is not known, it has been observed that this is a rather constant finding. Chesley[11] and Hayashi[12] performed uric acid clearance studies on patients with toxemia. It was observed that the blood level of the uric acid did not always correlate with renal clearance and that the severity of the disease did not coincide with elevation of the blood uric acid levels. In patients with toxemia Hayashi showed that the metabolic pool of uric acid was increased during pregnancy but not so much as in gout. It was assumed that the hyperuricemia observed during pregnancy was the result of metabolic dysfunction. He concluded that hyperuricemia alone was not an important factor in the etiology of toxemia of pregnancy.

In the present study 10 patients with pre-eclampsia were proved to have hyperuricemia which averaged 6.2 mg. per 100 c.c. of serum. These patients received no chlorothiazide.

TABLE II. HYPERURICEMIC INFLUENCE OF CHLOROTHIAZIDE IN NORMAL SUBJECTS

	FIRST POSTPARTUM DAY (BEFORE CHLOROTHIAZIDE)			FIFTH POSTPARTUM DAY (AFTER CHLOROTHIAZIDE)		
PATIENT NO.	SERUM URIC ACID (MG.)	HEMOGLOBIN (GM.)	HEMATOCRIT (MM.)	SERUM URIC ACID (MG.)	HEMOGLOBIN (GM.)	HEMATOCRIT (MM.)
1	3.3		40	4.0		43
2	4.2		47	6.9		50
3	3.6		44	4.8		44
4	4.5		40	7.0		50
5	5.4		42	6.6		43
6	3.8		45	6.0		47
7	3.2		46	6.0		52
8	3.5		38	6.1		43
9	6.6		47	7.7		47
10	5.2	9.7	39	5.0	9.6	39
11	5.2	12.2	40	6.0	12.1	42
12	3.8	11.5		6.2	10.8	
13	4.0	11.8		4.8	14.8	
14	3.8			6.2		
15	4.3			5.0		
16	4.2			5.4		
17	4.0			4.4		
Average	4.3	11.3	42.6	5.8	11.8	45.5
Average change				+1.5 mg.	+0.5 Gm.	+2.9 mm.
Percentage change				+35	+4	+7

In comparison, 4 patients with toxemia who had been treated with chlorothiazide as outpatients had an average uric acid level of 7.8 mg. Chlorothiazide was discontinued after delivery. Four days later an average of 4.8 mg. per 100 c.c. of serum was found, a decrease of 38 per cent. Hemoglobin was studied at the same time and it was found to rise from an average of 8.9 Gm. to 10.1 Gm. in 4 days, a 13 per cent increase.

Pre-eclamptic Patients Given Chlorothiazide (Table III).—For symptoms of pre-eclampsia 16 patients received chlorothiazide as intermittent therapy for 1 to 18 weeks before admission to the hospital. On the day following delivery examination of the blood demonstrated an average value of 5.7 mg. for uric acid; the average hematocrit was 43 mm. Averages of determinations of sodium were 133 mEq., of potassium 4.4 mEq., and of chloride 102 mEq.

Chlorothiazide was continued for 3 to 10 days after delivery and corresponding evaluations were made on the fifth postpartum day. The uric acid average was 6.5 mg., a 14 per cent increase. Unusually high uric acid levels were observed in 3 patients, with values of 12.6 mg., 11.2 mg., and 9.8 mg. Changes in average values for hemoglobin, hematocrit, sodium, potassium, and chloride were not significant.

From observations of this group variations in hyperuricemia did not correlate with hemoconcentration. Although the uric acid levels of the serum in the patients of this group were already elevated, they were further increased with the continued use of chlorothiazide.

Gynecologic Patients Given Chlorothiazide.—Six gynecologic patients were given 1,000 mg. of chlorothiazide daily. Prior to the institution of chlorothiazide the blood uric acid values averaged 3.7 mg. per 100 c.c. blood. After 5 days the average value was 4.3 mg., an increase of 16 per cent.

Corresponding values of hematocrit and hemoglobin were compared. Before chlorothiazide the hematocrit average was 43 mm. and the hemoglobin average was 12.3 Gm. After treatment the corresponding values and percentage changes were: hematocrit, 38 mm. (minus 12 per cent), and hemoglobin, 12.6 Gm. (plus 2 per cent).

TABLE III. HYPERURICEMIC INFLUENCE OF CHLOROTHIAZIDE IN TOXEMIA

PATIENT NO.	RECEIVED CHLOROTHIAZIDE AT TIME OF ADMISSION	FIRST POSTPARTUM DAY					FIFTH POSTPARTUM DAY				
		SERUM URIC ACID (MG.)	HEMATOCRIT (MM.)	SERUM Na (MEQ.)	SERUM K (MEQ.)	SERUM cl (MEQ.)	SERUM URIC ACID (MG.)	HEMATOCRIT (MM.)	SERUM Na (MEQ.)	SERUM K (MEQ.)	SERUM cl (MEQ.)
1	Yes	9.8					12.6				
2	No	3.8	45				5.2	47			
3	Yes	4.4	42				4.4	48			
4	Yes	7.1	41				5.2	45			
5	Yes	4.4	39				5.2	45			
6	Yes	7.2	43				9.8	49			
7	Yes	6.7	40				3.4	40			
8	Yes	4.3	47				5.0	45			
9	No	4.2	47	137	4.3	102	6.9	50	134	4.0	102
10	Yes	4.8	39	137	4.7	108	5.0	36	140	4.4	111
11	Yes	4.8	45	134	5.1	102	6.8	42	123	4.7	93
12	Yes	8.8	43	137	5.0	103	11.2	34	138	5.0	99
13	Yes	5.2	43	137	4.8	108	3.6	44	137	4.0	102
14	Yes	5.4		136	3.9	97	5.8		130	4.0	93
15	Yes	4.6		136	3.9	101	7.0		140	4.5	102
16	Yes	5.4		130	3.5	98	7.0		137	3.8	98
Average		5.7	43	133	4.4	102	6.5	43.7	135	4.3	100
Average change							-0.8	+0.7	+2	-0.1	-2
Percentage change							+14	+2	+0	-2	-2

Comment

After appraisal of the reasons for elevation of blood uric acid from the administration of chlorothiazide, it was observed that this occurred in both obstetric and gynecologic patients.

Hyperuricemia was not caused by hemoconcentration since uric acid levels rose out of proportion to the other constituents of the blood. The reason for the increase in uric acid concentration is not established by this study and whether this resulted from altered renal excretion of uric acid or dysfunction of metabolism is not known.

While the clinical importance of hyperuricemia resulting from chlorothiazide treatment appears to be minimal, its obstetric import lies in the confusion which may result from using serum uric acid levels as aids in diagnosis and prognosis in toxemia.

Results of this study suggest that chlorothiazide is a potent diuretic agent that is relatively free of toxicity. The equimolar excretion of sodium and chloride makes the drug comparatively safe for administration during pregnancy. Although the drug does not cure toxemia of pregnancy, our findings would put chlorothiazide in the group of drugs used as adjunctive in its treatment. These conclusions are similar to those of Finnerty and associates[13] who used chlorothiazide in patients with toxemia of pregnancy.

Conclusions

1. Chlorothiazide is of value in relieving the subjective symptoms of premenstrual tension.

2. Chlorothiazide is of adjunctive value in the empirical treatment of toxemia of pregnancy.

3. Chlorothiazide is a hyperuricemic agent.

Addendum.—After this paper was written, an article by Oren, Rich, and Belle, "Chlorothiazide (Diuril) as a Hyperuricademic Agent,"[14] mentioned the hyperuricemic influence of chlorothiazide and recommended that its use be avoided in cases of incipient gout.

The chlorothiazide used in this investigation was generously supplied through the courtesy of Dr. John R. Beem, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

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Discussion

DR. C. H. HENDRICKS, Cleveland, Ohio.—The authors have done a useful piece of work in observing the response of certain groups of obstetric and gynecologic patients to the drug chlorothiazide.

Of the 50 patients treated for premenstrual tension, they report that more than 60 per cent were "substantially improved." In this far-from-simple syndrome, with its month-to-month vagaries, it is comforting to have a drug which offers substantial help to 60 per cent of the patients. On the other hand, the symptom complex of premenstrual tension carries such a high "titer" of subjectivity that, had the authors chosen to run a control series with placebos, there would very likely have been at least a modest number of the controls who would also report "substantial improvement" of their symptoms after they had faithfully ingested their placebo medication exactly as directed by the physician.

Certain it is, however, that edema is an important component in many cases of the premenstrual syndrome. I would like to ask Dr. Stevenson if any large proportion of these patients were weighed daily in an effort to determine more directly the extent of the edema factor; and, if so, what was the degree of correlation between subjective improvement and the amount of weight loss while the subjects were taking chlorothiazide?

In the problem of pre-eclampsia, chlorothiazide proved to be an effective diuretic. Presumably some of the 35 patients who were managed solely on an outpatient basis would have required hospitalization if chlorothiazide or some other diuretic had not been employed. But a diuretic drug alone is not enough, since the authors point out that 8 patients had to be hospitalized before the combination of chlorothiazide plus the hospital regimen was able to control the advance of the disease; and in one further case all measures taken failed to prevent the onset of eclampsia.

The development of carbonic anhydrase inhibitors represents an advance in our knowledge of physiology, but we should remember that the use of carbonic anhydrase inhibitors is not necessarily a physiologic method since their action is based on the induction of a selective deficiency in normal renal function.

Even with the best pharmacologic agents used alone—and chlorothiazide is one of the best of such agents to date—we cannot achieve 100 per cent control over the sodium ion in pre-eclampsia. We remain far out on the periphery of a disease where we are concerned not only with renal function but also with a richly interwoven background of placental, dietary, social, and emotional factors.

It is gratifying to have a tool such as chlorothiazide available. Through our partial successes with symptom control, however, we must not lose sight of our larger goal: the goal of determining the etiology of pre-eclampsia and the prevention of the appearance of any of its manifestations.

ATTEMPTS TO MAKE AN "ARTIFICIAL UTERUS"*

Part I. The Adaptation of Blood Pumps and Oxygenator for This Purpose

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THE dramatic reduction of maternal mortality achieved in the past 20 years unhappily has not been accompanied by parallel reduction in fetal mortality. About 10 per cent of all pregnancies do not result in a living child. Much of this wastage is due to prematurity, although diseases of the newborn, such as hyaline membrane disease, atelectasis, and pneumonitis, and congenital defects as well as maternal diseases—notably toxemia, diabetes, and Rh sensitization—make significant contributions to this loss. Both obstetricians and pediatricians agree that the problem of reducing fetal wastage is one of the greatest challenges to their professions today. Admittedly, management of premature labor and care of the premature infant have been important contributions toward reducing this wastage, yet all must agree that there is much room for further progress.

In our opinion, refinements in the artificial kidney and the pump-oxygenator have placed in our hands a means of permitting salvaging many of these babies. A combination of blood pumps, a membrane-oxygenator, and, if necessary, an artificial kidney in a controlled environment which prevents heat loss, comprise equipment that may be designated an "artificial uterus." Members of the Department of Obstetrics and Gynecology and the Department of Artificial Organs of The Cleveland Clinic Foundation have been engaged in adapting equipment in current use, and in devising a new apparatus for a system of extracorporeal circulation that will sustain these handicapped babies until they have overcome their difficulties or have reached viability. This initial study will report only generalities; it will be followed by studies that will cover in detail specific facets of our work.

Objectives

By using a properly modified pump-oxygenator with or without an artificial kidney we believe that the following results may be achieved:

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A. Short-term perfusion of a newborn via the umbilical or other vessels, while correction of otherwise fatal conditions can be carried out, such as: inflation of atelectatic lungs or the washing out of hyaline deposits from the pulmonary alveoli.

B. Safer surgical and medical treatment of infants and of small children who have cardiac lesions or reversible renal disease.

C. Support of prematurely born babies until their own organs are able to sustain life, especially until their lungs are capable of providing sufficient oxygenation.

D. Under emergency circumstances, a possible application might be that of perfusing an extirpated, intact, pregnant uterus, and sustaining growth and development of the embryo to viability. Thus a fetus that would be doomed to death by therapeutic abortion, or that would be likely to die later on in pregnancy because of maternal toxemia, diabetes, or Rh incompatibility, could be salvaged, even though it would require sacrifice of the mother's uterus.

Requirements of Perfusion Systems for Babies

There must be:

1. Sufficient mechanical blood flow to balance the oxygen deficiency caused by the lack of oxygenation in the baby's own lungs. Vein-to-vein perfusion may suffice for this purpose.
2. Mechanical removal of CO_2 to maintain the pH of the circulating blood.
3. Inclusion of an artificial kidney if the baby's kidneys are not able to remove the waste products.
4. Support of heart action in case of cardiac failure. This could be done by vein-to-artery perfusion.
5. Intravenous nourishment if the intestinal tract is not functioning.
6. Maintenance of optimal temperature, and prevention of heat loss by radiation.

There must not be:

1. Uncontrolled changes in the blood volume. The blood volume of the extracorporeal circulation must either be constant or reflect the changes in the baby's blood volume.
2. Dehydration or overhydration of the patient. The use, in the oxygenator, of polyethylene or Teflon membranes that are impermeable to water and electrocytes will guard against this adverse condition. Inclusion of an artificial kidney makes it possible to correct the water imbalance and the electrolyte composition but it also introduces new problems.
3. Undue changes in temperature.
4. Damage of the blood by:

a. *Clotting.* The addition of heparin to the perfusing blood and the use of water-repellent glass and tubing are recommended.

b. *Hemolysis.* The use of constant-bore tubing, the avoidance of eddies and constrictions, and the use of atraumatic pumps are essential. Perhaps periodic or continuous removal of free plasma hemoglobin and dead cells from the circulating blood is another essential procedure to attain this objective.

c. *Loss of thrombocytes.* Generous heparinization of the perfusing blood is recommended.

d. *Loss of leukocytes.* Of possible importance although probably they are rapidly regenerated.

e. *Degeneration of proteins.* Use of suitable walls and membranes in the blood channels of the apparatus is essential.

f. *Infection.* Effective sterilization of the apparatus and use of a bacteriologically closed system is of extreme importance.

g. *Depletion of nutrients.* Intravenous injections of dextrose may be essential.

The problem of supplying well-oxygenated blood in an adequate volume and at desirable pressure and temperature under sterile conditions was approached in the following way: A 60 gallon polyethylene vat* was designed and con-

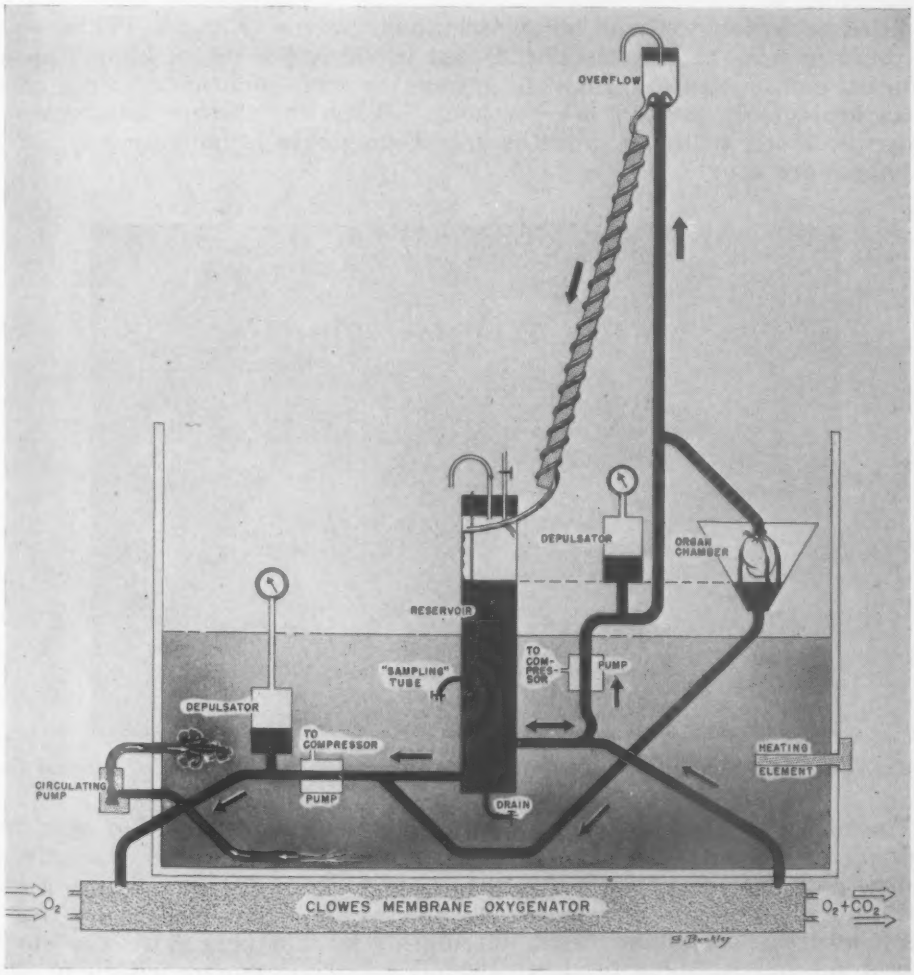

Fig. 1.—Diagram of the "artificial uterus."

structed. It was equipped with a thermostatically controlled heating mechanism, pumps, a reservoir, an overflow arrangement, supports for holding the subject as well as for an artificial kidney, and pumps for the perfusing fluid of the kidney. Outside of the vat was placed a Clowes membrane oxygenator and the air compression pumps. All of the elements were smoothly joined with Tygon tubing†

*American Agile Company, Bedford, Ohio.
†Polyvinyl chloride, U.S. Stoneware Company, Akron, Ohio.

with an inside diameter of 3/8 inch (Fig. 1). Great care was exercised in selecting components that would minimize trauma to the circulating blood. A constant-bore system is essential to attain a low rate of hemolysis. Coagulation of the blood is controlled with heparin.

Hemolysis

For long-term perfusions the pumps usually used in the pump-oxygenator and artificial kidney systems produce a prohibitive amount of hemolysis. We tested the Sigmamotor pump, the Leonards occlusive roller pump, the Hercik nonocclusive roller pump, the MacNiel-Collins pump and the Dale-Schuster pump and found that none were completely satisfactory. Therefore, two modifications of the Dale-Schuster pump were constructed in our laboratory and fitted with polyurethane tricusp-semilunar valves (Fig. 2). These pumps still produce some hemolysis (Fig. 3) but if 500 to 600 ml. of human blood is circulated continuously through the system the increase is only 1.3 mg. of free plasma hemoglobin per 100 ml. per hour. When the Clowes membrane-oxygenator is added to the system the free hemoglobin is increased by 3.2 mg. per 100 ml. per hour.

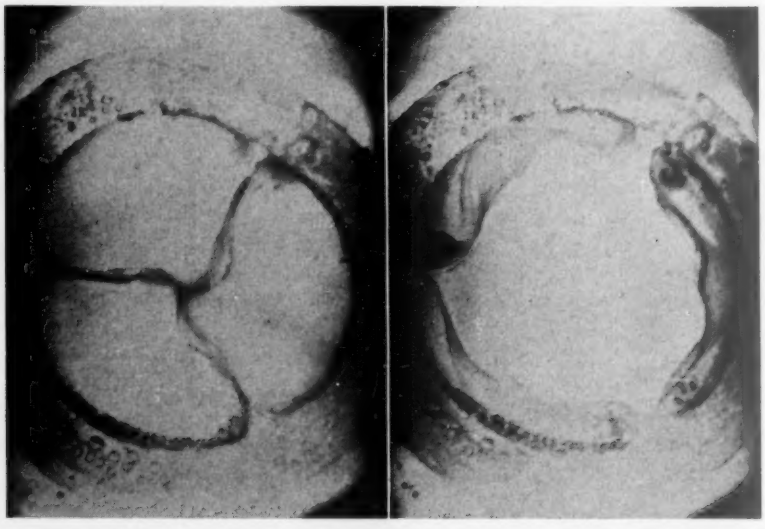

Fig. 2.—High-speed photographs of polyurethane tricusp-semilunar valves, closed and open.

The idea of "replacement transfusion" of specific amounts of new, fresh blood at intervals to prevent free hemoglobin accumulation was carefully pursued, and one of us, (J. J. C.) has worked out a formula which permits determining beforehand how much blood must be exchanged to control the amount of free hemoglobin in the circulating system (Fig. 4). The amount required for our machine is about 100 ml. per hour and is within practical limits even when the membrane-oxygenator is incorporated in the circuit. When we arrived at this point, we believed we were ready to test our apparatus on a living organ. We decided to use an organ rather than a fetus because the less complicated procedure was necessary for development of technique.

Testing of Equipment by Perfusion of Isolated Hearts

The heart has the advantage over other organs of being clean and of communicating its well-being by clearly visible beats. The experiments were

performed with excised hearts of dogs. The animal was heparinized and exsanguinated, and the blood used to prime the machine. As quickly as possible, the heart was removed and perfused, the overflow cannula from the machine being attached to the aorta. During perfusion the aortic valves

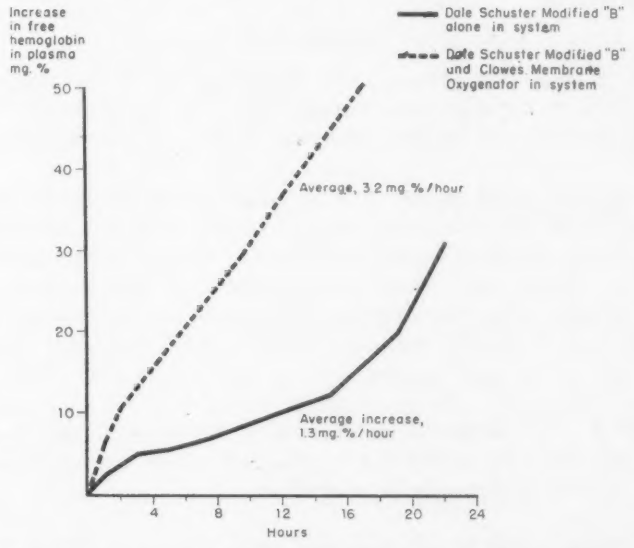

Fig. 3.—Graph of hourly increase in milligrams per hour of free plasma hemoglobin with modified Dale-Schuster pump alone and in combination with Clowes membrane-oxygenator.

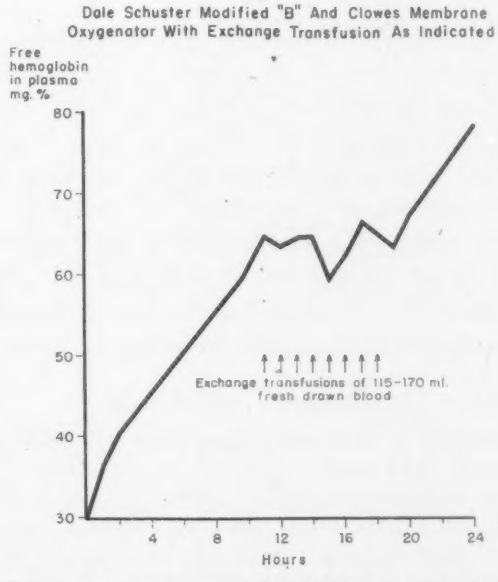

Fig. 4.—Graph showing effect of "replacement transfusions" on concentration of free plasma hemoglobin.

closed and the blood flowed through the coronary arteries. As the heart began to beat, the coronary blood returned through the sinuses to the right atrium and was expelled by the beating heart, mainly through the cut pulmonary artery. It was collected in a funnel, a part of the circuit, beneath the heart (Fig. 1).

In the first experiment the heart beat for 5½ hours, in the second for 7½ hours, in the third for 9½ hours, and in the fourth for 5 hours. In the

second experiment when the heart stopped beating it was found that all of the dextrose in the perfusing blood had been exhausted.

We are far from our goal, but we are convinced that carefully controlled extracorporeal circulation ultimately will offer an effective means of reducing reproductive wastage.

Discussion

DR. JOHN I. BREWER, Chicago, Ill.—The objective in the attempt to develop this device was an effort to increase fetal salvage, especially of premature infants. The frequently occurring problems of hyaline membrane disease and atelectasis come to mind immediately.

Premature infants might require a long period of "incubation." How this artificial device would work under such circumstances is, I believe, unknown, although the authors feel that eventually it may maintain normal function for weeks or even months. Costs of such therapy, I dread to contemplate. Short-term application of this device seems more practical and feasible in hyaline membrane disease. This device apparently could accomplish this with ease. Application to cardiac surgical procedure in infants seems feasible.

It is tempting to let one's imagination run wild in thoughts of possible applications. If this apparatus is attached to the nonpregnant uterus, with the perfusion of hormones and other substances, one might be able to elaborate upon the morphologic and physiologic aspects of menstruation, especially the mechanism of bleeding. If it were attached to the pregnant uterus, placental function might really be determined.

Obstetrics

PREGNANCY IN THE TUBAL INTERSTITIUM AND TUBAL REMNANTS*

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DURING a recent survey of 322 consecutive pathologically proved ectopic pregnancies at the Mayo Clinic, we found that 34 women had had 2 ectopic pregnancies each. This was 11.1 per cent of our series. Of this group of 34 women 4, or 11.7 per cent, had had 2 ectopic pregnancies in the same tube. This incidence, along with a recent interest in ultraconservative operations for ectopic pregnancy, led us to review our cases of pregnancy in the tubal interstitium and in tubal remnants. The latter group is included because we wish to stress the importance of complete rather than partial removal of a tube when there is any indication for surgical excision. These two groups composed 5.5 per cent of our series of ectopic pregnancies.

Interstitial Pregnancies

Wynne[13] stated that the first authentic case of interstitial pregnancy was reported as a necropsy specimen in 1801. The first report of this condition by an American was made in 1875 by Fitz.[5] Wynne reported that in 1893 Traub did a supravaginal hysterectomy for an interstitial pregnancy with recovery of the patient; this was the first reported survival of a patient with this condition. Shortly thereafter Tait incised a sac in an interstitial pregnancy, evacuated the conception, and drained the tube; this patient was the first reported to survive after a conservative operation for this type of ectopic pregnancy.

Interstitial pregnancies comprised 3.4 per cent of our series of ectopic pregnancies. Felmus and Pedowitz[4] reported an incidence of 4.7 per cent

*Read at a meeting of the Minneapolis and Minnesota Obstetrical and Gynecological Societies, Minneapolis, Minn., Oct. 2-4, 1958.

†The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

in their own series of ectopic pregnancies and an incidence of 2.7 per cent when they summarized various series reported in the literature.

For a specimen to be classified as an interstitial pregnancy, it should be noted that the round ligament is outside the gestation sac and occupies a position either lateral and inferior or anterior and inferior to it. In 3 of our 11 cases both the interstitial portion of the tube and the horn of the uterus were involved, making it impossible to determine the primary site of implantation. In these cases we are inclined to agree with Felmus and Pedowitz[4] who expressed the opinion that the term "cornual pregnancy" should more properly be reserved for pregnancy in a rudimentary horn of a uterus.

The symptoms varied from the complex vagaries of an unruptured ectopic pregnancy to the classic picture of a ruptured ectopic pregnancy with the patient in profound shock. The length of gestation varied from 4 to 32 weeks with an average of 10 weeks. None of our patients carried to term, though such cases have been reported.[6, 8]

TABLE I. INTERSTITIAL PREGNANCY

AGE (YEARS)	GRAVIDITY	PARITY	PREVIOUS OPERATION	ECTOPIC PREGNANCY, SIDE	OPERATION	SUBSEQUENT HISTORY
22	4	1	Appendectomy; left salpingectomy for ectopic pregnancy	Left	Wedge excision left horn	2 full-term normal deliveries
27	3	0	Left salpingo-oophorectomy; appendectomy	Left	Repair left horn	1 full-term normal delivery; 1 abortion
39*	4	3	Left salpingectomy and oophorectomy for dermoid cyst	Left	Total abdominal hysterectomy; right salpingectomy	----
36	5	3	Right salpingo-oophorectomy; appendectomy	Right	Total abdominal hysterectomy; left salpingectomy	----
33	4	3	Excision right ovarian cyst; appendectomy	Left	Vaginal hysterectomy	----
28	2	1	None	Right	Right salpingectomy and evacuation right horn	Full-term pregnancy, normal delivery; ectopic pregnancy on left, 5 years after operation
34	10	8	None	Left	Bilateral salpingo-oophorectomy	----
24	3	0	None	Right	Right salpingectomy	5 full-term normal deliveries
40	3	0	None	Right	Right salpingectomy	----
34	3	2	None	Left	Left salpingectomy	----
39	5	4	None	Right	Right salpingectomy	----

*This patient was pregnant between the time of initial operation and development of interstitial pregnancy.

The data are summarized in Table I. The age range of the group of patients was 22 to 40 years with an average of 32.3 years. This represents the average childbearing group without any predilection for a particular age. The number of pregnancies varied from 2 to 10 with an average of 4.1 per

patient. The average number of living children, however, was 2.2 per patient with a range of 0 to 8. Of the group, 5 had had previous pelvic operations (one for an ectopic pregnancy in the same tube). Salpingectomy had been done previously in 4 cases, none of which included wedge resections of the uterine horn. Only one of these patients (Table I, footnote) had any pregnancies between the time of the initial operation and the interstitial pregnancy. The initial pelvic operation had involved the removal of the homolateral ovary in 3 instances. The clinical impression was ectopic pregnancy in 9 cases, uterine fibroids with an ovarian cyst in one instance, and ruptured uterine pregnancy in one case.

The operative procedures for the interstitial pregnancies included salpingectomy with wedge resection of the horn in 6 cases, hysterectomy in 3 cases, bilateral salpingo-oophorectomy in one case, and repair of a rent in the horn where a tube had ruptured in one case. Of the 7 patients who retained at least one ovary, one tube, and the uterus, 4 became pregnant subsequently and were delivered of at least one full-term infant via the birth canal without incident. One of the 4 patients had an ectopic pregnancy in the contralateral tube 5 years later.

Eight of the patients required the use of blood or plasma substitutes. Each of these required an average of nearly 3 units to counteract the state of shock.

There were no maternal deaths.

Pregnancy in Tubal Remnants

The 7 patients having pregnancy in tubal stumps formed 2.1 per cent of our series of ectopic pregnancies.

TABLE II. TUBAL REMNANTS

AGE (YEARS)	GRAVIDITY	PARITY	PREVIOUS OPERATION	ECTOPIC PREGNANCY, SIDE	OPERATION
25	4	0	Partial left salpingectomy for ectopic pregnancy	Left	Left salpingectomy; appendectomy
42	2	0	Right salpingectomy for ectopic pregnancy	Right	Right salpingo-oophorectomy; left salpingectomy
30	3	2	Right salpingectomy for ectopic pregnancy; left tube tied for sterilization	Right	Right salpingo-oophorectomy; left salpingectomy
40	8	6	Left salpingectomy for ectopic pregnancy; partial right salpingectomy for sterilization	Right	Right salpingo-oophorectomy
31	7	6	Left salpingectomy; uterine suspension	Left	Total abdominal hysterectomy; bilateral salpingectomy
32	4	2	Bilateral partial salpingectomy for sterilization	Right	Total abdominal hysterectomy; bilateral salpingo-oophorectomy
32	4	3	Bilateral partial salpingectomy for sterilization	Right	Right salpingo-oophorectomy

The data are summarized in Table II. The average age of these patients was 33.1 years. The number of pregnancies that each reported ranged from 2 to 8 with an average of 4.5 per patient. The number of living children ranged from 0 to 6 with an average of 2.6 per patient. Of this group, 4 had had previous ectopic pregnancies; 3 of the 4 had the second ectopic pregnancy in the same tube, and 2 had had the second tube partially resected for sterilization purposes at the time of operation for the first ectopic pregnancy. Two other patients had partial salpingectomies for sterilization and one patient had had partial salpingectomy for an unknown reason at the time of uterine suspension. None of the patients had salpingectomies that had included the interstitial portion of the tube. In all cases the ectopic pregnancies had developed in the portion of the tube that remained external to the uterus. The preoperative diagnosis was ectopic pregnancy in 5 cases, myoma of the uterus in one case, and pelvic tumor in one case. Only one of the patients was left with a patent tube and we have no follow-up data on her.

Comment

The diagnosis of ectopic pregnancy is difficult at times, but constant awareness of its occurrence, even when the patient is reported to have had both of the tubes removed, will lead to earlier diagnosis and treatment. Eleven patients of this series had ectopic pregnancies in tubes that had been operated on previously.

The exact etiology of an ectopic pregnancy in many cases remains obscure. The commonly enumerated etiological factors are previous pelvic operation, transmigration of an ovum, tumors, congenital deformities, pelvic inflammatory disease, and, associated with these, sterility.

The previous pelvic operations can be divided into two categories: operations having to do with the tubes, and other pelvic operations such as those involving ovarian cysts, oophorectomies, myomectomies, uterine suspensions, and so forth. Twelve of the group had had previous pelvic operations: 5 of them reported previous salpingectomies for ectopic pregnancies; 6 had had previous partial salpingectomies (3 for sterilization purposes), and one had had an ovarian cyst removed.

Transmigration of an ovum can be either internal or external. In 3 cases transmigration had taken place, the homolateral ovary having been removed previously. In all 3 cases interstitial pregnancies had ruptured preoperatively, thus making it impossible to determine whether or not there had been an external opening in the tubal stump to allow the ovum to enter.

There were no cases in which the etiology of the ectopic pregnancy could be attributed to tumors, intrinsic or extrinsic, or to congenital deformities such as diverticula or accessory ostia.

None of the 18 patients with pathologically proved ectopic pregnancies gave a history of pelvic inflammatory disease and at operation there were no gross findings suggestive of previous infection.

Sterility in its true sense, that is, the inability to produce a living child, was present in 5 cases. These patients had all been able to conceive, each having had 2 to 4 pregnancies, but none had produced a living child. This problem is closely allied with the next group.

There were 4 cases in which none of the factors mentioned heretofore were present. Physiologic malfunction might be listed as the etiological factor in these cases. This could be either in the transportation of the ovum through the tube or in the process of development of the burrowing mechanism of the fertilized ovum.

The transit of the ovum in human beings has been a source of much speculation and investigation. A fluid current and a sucking movement toward the uterine cavity have been shown to exist.[12] That the current is produced by lymphatic absorption, as stated by Dubreuil,[3] or that it is caused by peristalsis, by ciliary action, or by any combination of these movements is without substantiation. Doyle[2] has observed the tubes in women at the time of ovulation and has found peristaltic waves occurring 6 to 7 times per minute; however, within 36 to 48 hours the number had increased to 10 to 12 per minute. He also noted a hypersecretion and hyperemia of the fimbria of the tube at the time of ovulation. When not functioning properly, any or all of these physiologic processes could contribute to the extended stay of the fertilized ovum in the tube. This would allow the ovum to develop to the trophoblastic stage which would then lead to implantation in the tube despite the absence of a rich decidua. One might also postulate an acceleration in the development of the ovum to the trophoblastic phase, so that despite normal transportation mechanisms the ovum burrows into the tubal wall instead of the uterine wall.

The treatment of ectopic pregnancies, regardless of their location, is surgical. We are of the opinion that when there is an indication for removal of the tube, its interstitial portion and a wedge of the surrounding horn should also be excised. Had this been done initially in this group of patients, 11 of them probably would not have been subjected to a second operation. Bickerstaff[1] has reported a case in which a subsequent pregnancy occurred at the site of removal of a wedge of the horn concurrent with salpingectomy. The patient required a second wedge resection when an intramural pregnancy was found at the old operative site. Reports of such cases are fewer than those of pregnancies in tubal stumps and interstitial regions following partial salpingectomies. There was no trouble with scars in repaired uterine horns but occult rupture has been reported at such sites by Malfetano and others.[7] Malfetano goes so far as to state that hysterectomy is the operation of choice unless the woman is nulliparous or unless the duration of pregnancy is less than 10 weeks.

Turner and Ferguson[11] have reported a recurrent ectopic pregnancy at the site where an earlier ectopic pregnancy had been shelled out. Tompkins[9] reported a series of 12 cases in which the patients were treated by splitting the tube; subsequently he[10] reported that one of these patients had been delivered of a full-term living infant and one patient had had a subsequent ectopic pregnancy in the operated tube. We feel that less than a complete salpingectomy is in order only when there is a strongly expressed desire on the part of the patient to have further pregnancies. Total abdominal hysterectomy may be indicated when there has been destruction of both tubes.

Summary and Conclusions

From a group of 322 ectopic pregnancies previously studied, 11 cases of interstitial pregnancy and 7 cases of pregnancy in tubal stumps have been presented.

The etiological factors in ectopic pregnancies often remain obscure, but when they are known they commonly include transmigration of an ovum, previous pelvic operation, congenital deformities, pelvic inflammatory disease, tumors, and sterility.

The treatment of tubal pregnancy is total tubal resection with removal of a wedge of the uterine horn in cases where the second tube is intact. When

there has been destruction of both tubes, total abdominal hysterectomy may be in order. Only when there is an extreme desire for pregnancy and a malfunctioning second tube do we feel that salpingostomy is warranted.

Four of the seven patients who had wedge resections of the uterine horn and who had retained at least one ovary and one tube were subsequently delivered of full-term infants vaginally without incident.

There were no maternal deaths in this series.

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UNILATERAL TUBAL TWIN PREGNANCY

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THE first report of this most unusual kind of twin ectopic pregnancy was made in 1891 by De Ott.[2] Since then Arey[1] and others[3, 6] have reviewed the literature, and through 1957 at least 79 authentic cases have been reported compared to over 114 cases of bilateral simultaneous tubal pregnancy.[4, 5, 7] The following is a case report of another unilateral tubal twin pregnancy.

B. J. M., No. 125761, a 24-year-old white woman, gravida iii, para ii, was admitted to Saginaw General Hospital on July 16, 1958, with vaginal bleeding and crampy abdominal pain of 6 hours' duration. One week previously she had vaginal spotting which cleared spontaneously and on the day prior to admission she noted painless vaginal bleeding. She had normal 28 day cycles with a 5 day flow and her last normal menstrual period was on May 22, 1958. In March and April her menstrual periods lasted 2 days each. She had otitis media one week prior to admission and was taking oral penicillin. There was no history of twins in the family.

The temperature was 98.8° F., pulse 92, respiration 24, and blood pressure 122 systolic and 64 diastolic. On examination of the abdomen, suprapubic tenderness was noted. The uterus was not palpated. Pelvic examination disclosed dark blood in the vagina and a soft cervix with a closed os. The uterus was enlarged to that of a 2½ months' gestation. No masses were felt in the adnexa. The hemoglobin was 12.6 Gm., hematocrit 38 per cent, leukocytes 10,900 with 80 per cent neutrophils and 20 per cent lymphocytes. The urinalysis was normal.

On July 17, the abdominal pain persisted and the patient developed pain in the right side of the chest, aggravated by deep inspiration. There was no tenderness in the calves and a chest x-ray was normal. On July 18, the hemoglobin dropped to 10.0 Gm. She was operated upon that evening.

At operation the abdomen was found to be filled with blood and the right Fallopian tube showed complete obstruction at the fimbriated end. The uterus was enlarged and covered with fine fibrinous adhesions. The left Fallopian tube was elongated and distended at the distal third. This was resected and the fimbriated end of the right tube was opened and sutured back, leaving a patent tube. Postoperatively she had a "spinal headache" which cleared spontaneously.

Pathological Examination.—

Gross (Fig. 1): The specimen was a Fallopian tube which had been partly dissected. Its over-all dimensions were 7.5 by 4.2 by 2.5 cm. The fimbriated end was partly obliterated and there was extensive hemorrhage on the surface of the tube. In the lumen and extending into the wall was a placenta measuring 4 cm. at its greatest diameter. Attached to this was an umbilical cord measuring 2.5 by 0.3 cm. and attached to the cord was a normally developed fetus with crown-rump length of 3.5 cm. and crown-heel length of 4.0 cm. The sex could not be determined. Only one placenta could be definitely identified. Sections perpendicular to the lumen of the tube showed chorionic tissue to have invaded deeply through the wall and extended into the serosa.

Separately received was a macerated fetus measuring 2.5 cm. long, which had been decapitated. This fetus and its cord were attached to the placenta but became disengaged and decapitated when the specimen was opened in the operating room for the fetuses to be baptized.

Microscopic: The smaller fetus showed extensive degenerative change but various organs were identified. In the Fallopian tube were large immature chorionic villi some of which showed central hydropic degeneration. The villi infiltrated the wall of the tube and penetrated the muscle and serosa in some fields. There was heavy decidual reaction within the tube and in some fields decidual cells were present within the blood vessels. The wall of the tube was very thin and showed infiltration by neutrophils in several places.

Diagnosis.—Hemorrhagic ectopic tubal pregnancy with twin fetuses. Chronic salpingitis.

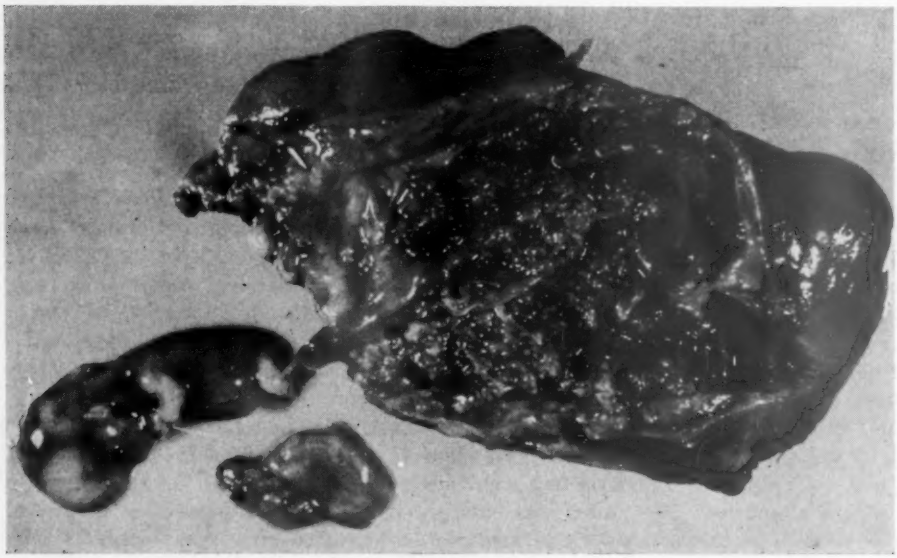

Fig. 1.

Summary

Unilateral tubal twin pregnancy is a rare occurrence. Through 1957 at least 79 authentic cases have been reported. We believe that this case report brings the total to 80.

We are grateful to Dr. L. Bruggers for allowing us to report this case.

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TERM TUBAL PREGNANCY WITH SURVIVAL OF MOTHER AND INFANT

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ADVANCED tubal pregnancy is a very rare condition, being the least common type of advanced ectopic pregnancy. The Fallopian tube cannot withstand much stretching; termination of the pregnancy usually occurs long before term.

McElin and Randall[8] collected and reported a series of cases of advanced tubal pregnancy, including one of their own. In 9 of this series both mother and baby survived and only 6 of these were full-term infants. Gustafson and associates[2] also reported one such case (Table I).

TABLE I. REPORTED CASES OF ADVANCED TUBAL PREGNANCY

AUTHOR	YEAR	AGE OF MOTHER	GRAVIDITY	PARITY	DURATION OF GESTATION	SIDE
Schmit[12]	1913				Term	
Krasnopolski[5]	1913					
Smith[14]	1920	32	iv	iii	9 months	
Lichtenstein[7]	1920	34	ii	i	Term	Right
Hoehne[3]	1923	30			7½ months	Right
Lazarevic[6]	1929	36	i	0	7 months	Left
Wallau[15]	1942	22	i	0	Term	Left
Casas[1]	1946	43	iii	ii	Term	Left
Ross and Weekes[11]	1948	32			Term	Left
Gustafson, Bowman, and Stout[2]	1953	24	i	0	Term	Right

B. D., Hindu, aged 32 years, was admitted at the A.H.M. & Dufferin Hospital, Kanpur, on June 8, 1957, complaining of lower abdominal swelling gradually increasing for the past 5 months, amenorrhea for 5 months, and pain all over the body for 10 days.

On abdominal examination, there was a swelling rising from the pelvis and extending to the umbilicus, more toward the left than the right side. It was ovoid with the long axis lying longitudinally in the abdomen. It had well-defined margins and was firm in consistency and slightly tender. It was movable from side to side but not from above downward. On vaginal examination, a mass feeling like a tense cyst and extending up to the umbilicus was felt in the left and posterior fornices. The uterus could be felt separately from this mass, being anteverted, mobile, slightly bulky and firm in consistency. A diagnosis of ovarian cyst was made.

She was admitted for laparotomy after a month. At this time the swelling had increased in size, extending an inch above the umbilicus, and on vaginal examination the uterus could not be felt separately from the mass. X-ray of the abdomen showed a fetus corresponding in size to the period of amenorrhea.

She was admitted in labor on Sept. 12, 1957. The pregnancy now extended from the pubic symphysis to 2 fingerbreadths below the xiphoid. The whole abdomen was tense

and the fetal parts were not easily definable. The fetus was lying in transverse position with the head in the left flank. The fetal heart sounds were clearly audible. On vaginal examination, the cervix was neither dilated nor taken up and was quite firm. The presenting part was so high that it could not be reached.

A cesarean section was decided upon. When the abdomen was opened, the parietal peritoneum was found to be adherent to the gestational sac over an extensive area. The adhesions were swept aside and the sac visualized. This looked grayish in color, nonmuscular and thin walled. A bladder flap could not be identified on the lower uterine segment. Therefore, the sac was incised at its upper part. A living female child was extracted by the vertex. When an attempt was made to deliver the placenta, no plane of cleavage could be found and only then was it realized that the pregnancy was intratubal.

The omentum was adherent to the upper portion of the sac while the sac itself was adherent to the abdominal wall at the left lumbar region. The sac was attached to the left cornu of the uterus by a pedicle about 5 cm. wide. The left tube and ovary could not be identified, while the right appendages were normal. The uterus was the size of an 8 weeks' pregnancy and was lying below and behind the gestational sac. The placenta was completely enclosed in the sac, being situated in its posteroinferior aspect. Left salpingectomy was performed, with removal of the sac and placenta en masse.

Macroscopic Appearance of the Specimen.—The placenta was normal in size and was situated 2 inches above the root of the pedicle. Its fetal surface only could be seen and this was covered by amnion. The cotyledons at the maternal surface could not be seen as they were covered by the sac wall formed by the grossly expanded tube. The maternal surface of the placenta was so intimately adherent to the sac that the two could not be separated. The sac was grayish in color with white and yellow patches on its outer wall due to necrosis resulting from distention and pressure. The wall was very thin, being only ½ to ¾ cm. thick.

Comment

McElin and Randall[8] considered that in term or near-term tubal pregnancy, without rupture of the tube, the fetus and placenta should be enclosed within the sac completely and no other pelvic or intra-abdominal organ should be involved in the formation of the sac and that salpingectomy alone should be the curative therapy. The findings in our case here reported were exactly similar and the same line of treatment was adopted.

The diagnosis of advanced extrauterine pregnancy can be made only when its possibility is kept in mind in a case where pregnancy presents unusual features. In the case reported during the first visit of the patient, the significance of the presence of a cystic swelling separate from the uterus and corresponding in size to the period of amenorrhea was not appreciated as indicative of an extrauterine or intratubal pregnancy. A month later, during the second visit of the patient, the increased size of the gestational sac had masked the uterus to such a degree that the two could not be felt separately and a diagnosis of normal intrauterine pregnancy was considered.

The diagnosis of term tubal pregnancy is nearly always made at laparotomy and our case was no exception.[2, 8, 10, 11] The usually described diagnostic aids for advanced extrauterine pregnancy are seldom of any help in practice. Hysterography can be employed in only those cases where the fetus is dead.

Tubal pregnancy is always associated with an intact sac, and therefore pregnancy swelling is mobile and the fetus ballotable to a much greater degree than is the case in extrauterine pregnancy without a sac, e.g., secondary abdominal pregnancy. Treatment is simpler in the case of pregnancy with a

sac, as the sac can be removed en masse with the placenta; while in the case of pregnancy without a sac, the placenta may have to be left behind with attendant complications.

This case has yet another interesting feature. The placental site was the posteroinferior aspect of the tube, i.e., the area of attachment of mesosalpinx, which is in agreement with the view of Schumann,[13] who considers this as the only feasible site if the pregnancy is to advance to later months; in his opinion this is the most vascular area in the Fallopian tube and therefore can meet the increasing demands of the growing fetus.

Attempts at classification of tubal pregnancy into fimbrial and interstitial depending upon the site of nidation of the fertilized ovum have been made, but it is felt this classification is of only academic interest.

Summary

1. A case of full-term tubal pregnancy in the left Fallopian tube is described. The pregnancy was terminated by abdominal delivery, a left salpingectomy was performed, and the sac with the placenta removed en masse.

2. The literature on full-term intratubal pregnancy is reviewed. This is believed to be the eighth case recorded in literature where both mother and baby survived.

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PREGNANCY IN SICKLE CELL ANEMIA, SICKLE CELL-HEMOGLOBIN C DISEASE, AND VARIANTS THEREOF

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SICKLE cell disease coincident with pregnancy has provoked increasing interest among many obstetricians during the last decade and various attitudes of concern or optimism have been the result of their observations. For instance, a review of the experience in this hospital in 1949 by Anderson[1] suggested a more favorable outlook for pregnant women with sickle cell anemia than seemed indicated by numerous previous reports. In all of these reports patients whose erythrocytes assumed a sickle shape were felt to have either sickle cell anemia or the sickle cell trait, depending on the intensity of the sickling and on other less specific features. More adequate differentiation of the sickle cell disease was simply impossible until fairly recently, but credit must be given to the early writers for recognizing that patients with apparently identical diagnoses sometimes responded quite differently to pregnancy. Gestation was uneventful for certain members of each group while others became gravely ill. The introduction of filter paper electrophoresis in 1952 furnished a practical method for identifying genetic hemoglobin patterns and emphasized the unreliability of microscopic identification of sickle cells. With this accurate method of classifying the hemoglobin diseases now available, it has become necessary to reconsider the problem of sickle cell disease in pregnancy. As early as 1954 it was suggested by Smith and Conley[2] that pregnancy offered greater hazards to patients with a combination of sickle hemoglobin and hemoglobin C. More recent reports seem to have added weight to this concept even though some authors have felt that their studies were inconclusive. An example of this is the survey by Molina and Marks[3] of patients at the Charity Hospital of Louisiana with known electrophoretic hemoglobin patterns. Three deaths occurred relative to pregnancy in patients with electrophoretic patterns known to the authors. All 3 had sickle cell-hemoglobin C disease. Still another current article from Ghana[4] tells of sudden death in 3 women with this same pattern. Very rarely has mention been made of serious maternal complications associated with true homozygous sickle cell anemia. With the feeling that the prognosis suggested by all these previous reports might be substantiated, we have undertaken the present study.

Since filter paper electrophoresis was begun in this hospital in 1952,[5] the series of Negroes with significant hemoglobin abnormalities has grown steadily. This laboratory procedure affords a simple, rapid, and inexpensive method of identifying normal hemoglobin A, sickle S, hemoglobin C, and fetal hemoglobin F. Of these, only hemoglobin S causes sickling of red cells. Only when the homozygous genetic pattern S-S has been found is the term *sickle cell anemia* applied. Combinations of sickle hemoglobin with other types make up the *sickle cell variants.* Of these, *sickle cell-hemoglobin C disease* (S-C) is of particular importance. The morphologically abnormal erythrocyte of thalassemia (Cooley's anemia) may be found in persons also harboring sickle cell hemoglobin. This condition is called *sickle-thalassemia.* Homozygous *hemoglobin C disease* (C-C) is the last condition to be included and like the others is limited, for practical purposes, to persons of negroid descent. Formerly the term "trait" was used for any patient with sickling whose benign clinical course or lack of typical lesions differentiated them from others with true sickle cell anemia. Now the word *trait* refers to the presence of sickle hemoglobin or hemoglobin C with normal hemoglobin. Forty-six adult women with electrophoretically proved sickle cell anemia, sickle cell-hemoglobin C disease, sickle thalassemia, and homozygous hemoglobin C disease have been evaluated on the hematological service of this hospital.* By reviewing the obstetrical history in 42 of these patients with hemoglobin disease, we have sought some regularity.

Material

Random sampling of significant numbers of Negroes by several clinics in the United States has established the incidence of the sickle trait (S-A) as about 8.4 per cent.[6] Hemoglobin C trait (C-A) has been found in about 2.1 per cent. The occurrence of sickle cell anemia in 0.7 per cent and sickle cell-hemoglobin C disease in 0.15 per cent of the groups studied is several times what one would statistically expect. Among our 42 women with adequate history, 15 had sickle cell anemia (S-S) and 18 had sickle cell-hemoglobin C disease (S-C). Two other patients in each group have been seen here but are not included because of incomplete obstetrical histories. Sickle thalassemia has been found in 5 adult women and homozygous hemoglobin C disease (C-C) in 4 others. The disproportion between the number of patients with the S-S pattern expected and those found emphasizes the frequency with which sickle cell anemia becomes critical during childhood. Some of the patients in every group have never been pregnant. Actually, the number of deliveries in most of the categories was less than expected among the 8,428 nonwhite deliveries at the Johns Hopkins from 1952 through 1957. This implication that fewer women with sickle cell disease become pregnant, or that the diagnosis is sometimes missed will be considered later. In reviewing the available material it seems reasonable to question what effect gestation has upon women with hemoglobin abnormalities and conversely how these diseases may alter the expected course of pregnancy and delivery. Both of these, of course, bear directly upon the maternal and fetal outlook.

*A much larger group of patients with sickle trait (S-A) is omitted because this condition is so often unrecognized and because no common obstetrical problems have been noted.

TABLE I. OBSTETRICAL SUMMARY

CASE	J. H. H. HIST. NO.	SYMPTOMS BEFORE PREGNANCY	SYMPTOMS DURING PREGNANCY 1	2	3	4	5	6	7,8,9	AGE LAST PREGNANCY	STERILIZATION	SYMPTOMS CONTINUING AFTER LAST PREGNANCY	COMMENT
Sickle Cell Anemia.—													
1	103460	ACP	A	A	A	A	A			24	T.L.		
2	297816	ACP	AP	AP	A	A	A			33	T.L.	AP	
3	575769	ACP	A	A	A					33	X	APC	
4	445803	ACP	ACP	ACPI						24	T.L.	APC	Infarction attributable to thrombophlebitis
5	247844	ACP	A	A						22	T.L.	APC	
6	687792	AP	AI							34		AP	Mild symptoms throughout life
7	696906	ACP	A							27		APC	Questionable abortion
8	100565	ACP	A							20		APC	Involuntary infertility
9	420348	ACP	A							24		APC	Mild symptoms, involuntary infertility
Sickle Cell-Hemoglobin C Disease.—													
10	558945	O	O	O	O	O	O	O	O	32	T.L.	O	
11	305141	O	O	O	O	A	CPI	PD		26			
12	127304	API	O	O	A	ACP I	AP ID			26		PI	Symptoms between final pregnancies
13	281428	P	PA	A	APC PID					26		P	Symptoms between final pregnancies
14	379041	O	O	O	AP ID					41		O	
15	706137	O	A	A	AP ?I					24		O	
16	174945	O	A	A?I						22		O	

17	377778	O	O	O		28		O	
18	257485	AP	CPI	?		16		O	Survived delivery elsewhere
19	221373	P	O	O		21		O	
20	503965	APCI	CPI			17	T.L.	AP	
21	611651	AP?C	AP			19		?	
22	455063	P	A			23		AP	
23	796187	O	O			18		O	Spontaneous abortion
24	599312	O	O			?		O	Aged 74, never had symptoms
25	786500	O	O			23		O	History of hematuria
Sickle Thalassemia.—									
26	464441	AP	A	A	A	29		A	
27	527370	AP	A			32		A	
28	596738	O	O			O		O	Died aged 59, coronary artery disease
Hemoglobin C Disease.—									
29	562633	A	O	A	A	24		A	
30	224390	O	O	O	A	32	T.L.	A	
31	354288	O	O	A		31	T.L.	A	

Legend:

O, No symptoms referable to sickle cell disease.
A, Anemia with a hematocrit value of 30% or less.
C, Hemolytic crisis with a rapid fall in hematocrit value of 6% or more. Usually accompanied by increased bone or abdominal pain.
P, Bone pain.
I, Infarction or embolization of lung or other major organ.
D, Died.
T.L., Tubal ligation.
X, X-ray sterilization.

Note.—Of the patients presented here, Cases 11, 12, 13, 16, 18, 19, 20, 21, 24, 26, and 27 were included in the 1954 report by Smith and Conley.[2]

Effect of Pregnancy Upon Hemoglobin Disease (Table I)

Sickle Cell Anemia.—Every one of the women with sickle cell anemia (S-S) had been anemic before pregnancy and all had experienced crises characterized by abdominal and/or joint pain. Such well-known clinical features as disproportionately long legs, hyperextensile fingers, leg ulcers, cardiomegaly, or bone changes facilitated the diagnosis in most. Anemia and recurrent hemolytic crises were common and many had suffered infarctions in various organs. Most were chronically ill throughout their lives. It is not surprising that only 9 out of our 15 adult patients with S-S hemoglobin became pregnant. During these pregnancies no increase in the severity of most symptoms was noted. Not only did such lesions as leg ulcers, bone defects, and cardiomegaly remain unchanged, but the frequency and severity of crises failed to increase. Anemia during any pregnancy is difficult to evaluate, but particularly so in women who have spent a lifetime being transfused or treated in other fashions. Increasing anemia, often with jaundice, necessitated transfusion in 7 of our 9 gravidas. Only one (Case 4), however, suffered a true hemolytic crisis. Interestingly enough, this same patient not only experienced bone pain with a hemolytic crisis at term in her first pregnancy, but both recurred in the thirty-second week of her second pregnancy, to be followed one week later by spontaneous delivery of a stillborn fetus. Pregnancy cannot be considered innocuous in sickle cell anemia for even though crises may be no more frequent, anemia persists and blood transfusions themselves are potentially hazardous.

Pulmonary infarction developed in Case 6 in the sixth month of gestation but was not accompanied by bone pain and was in fact believed by some to be pneumonia. In Case 4 leg pain and pulmonary infarction occurred 15 days after delivery and were attributed to embolization from the bilateral thrombophlebitis which developed after tubal ligation.

It is difficult to interpret from recorded data or to convey to others the true degree of morbidity, but in only one case of sickle cell anemia (Case 6) did an apparently critical situation develop during pregnancy. The infrequency of painful hemolytic crises during pregnancy in women who had previously experienced many such episodes is particularly interesting.

Sickle Cell-Hemoglobin C Disease.—Turning from the essentially benign obstetrical pattern in sickle cell anemia, quite a different picture was found in the 16 patients with sickle cell-hemoglobin C disease (S-C) who experienced pregnancy. One of the most interesting observations in the entire study was the frequency with which this disease lay dormant until pregnancy. Once the anemia became overt, serious complications, even death, often occurred.

Stigmas which are encountered in sickle cell disease are found with much less frequency in the sickle cell variants. Only 4 of our 16 women with sickle cell-hemoglobin C disease were known to have had a hematocrit value of 30 per cent or less before pregnancy. When initially examined during pregnancy the hematocrit level averaged 34 per cent. In only 6 others was the presence of a sickle cell disease recognized before pregnancy (Cases 12, 18, 20, 21, 23, 25). Others had experienced abdominal or bone pain possibly related to the disease but these symptoms had prompted no specific diagnosis.

During the first two-thirds of pregnancy complications occasionally occurred, but were no more common than in nonanemic patients. Increasing anemia in the third trimester developed in over half of the women with the S-C pattern (Cases 11-16, 18, 20, 21) and often prompted the first specific

diagnosis of sickle cell disease. The fall in the hematocrit level was precipitous and severe enough to be termed a hemolytic crisis in 5. Others experienced a drop in hematocrit value of 3 to 6 per cent. Transfusions were given to all these patients and to several others who had no increasing anemia.

Two other complications occurred near term and were often accompanied by profound deterioration in the patient's condition. Any catastrophe was invariably preceded by bone pain with or without pulmonary infarction. Severe pain developed in half of all the women in this group and was described as "low back pain" or "bone pain" in the extremities. Joint pain was only occasionally specified and occurred in both the arms and the legs. While these pains may have been the most distressing complication to the patients, they have been of less practical significance than anemia or particularly pulmonary infarction.

Pulmonary infarction was diagnosed in 6 of the 16 patients and strongly suspected in 2 others. In every instance this complication was preceded by some degree of anemia and bone pain and occurred during the final trimester of pregnancy. Except for Cases 20 and 11, all were near term and these 2 patients became ill during the seventh month. Of these 6 patients in whom signs of acute pulmonary infarction developed, 3 died and still another was acutely ill. In some, dyspnea, with or without tachycardia, and chest pain were the only clinical findings. In others, overt infarction with fever, tachypnea, tachycardia, chest pain, and hemoptysis developed. Response to this catastrophe varied from complete recovery to death. No other complication which was observed in this group of pregnant women with sickle cell disease was fraught with more danger than infarction of the lung.

The triad of anemia, bone pain, and pulmonary infarction emerges as the most common sequence of complications in pregnant patients with sickle cell-hemoglobin C disease. Similar events are frequent in sickle cell anemia but begin early in life and recur until death, apparently made no worse by pregnancy.

Sickle Thalassemia.—Because of the variability of sickling in the peripheral erythrocytes, this condition may go unrecognized throughout life. Of the 5 patients studied with this condition 3 became pregnant and 2 developed increasing anemia just at term. Neither of these became acutely ill and gestation continued normally in other respects. The third patient was first seen at the age of 50 and had never had symptoms of anemia.

Hemoglobin C Disease.—Even the homozygous form of this hemoglobin abnormality may not be suspected since erythrocyte sickling does not occur. The present study includes 4 women of this type although others are known throughout the city. In 3 of these 4 women eight pregnancies were reviewed. Rapidly increasing anemia near term in 2 patients necessitated transfusions and suggested the need for further investigation, but more serious consequences were absent.

While the total number of these less common hemoglobin abnormalities is small, it seems at this time that pregnancy usually causes no greater complication than increasing anemia.

Effect of Hemoglobin Disease Upon Pregnancy

Just as pregnancy has apparently caused changes in the clinical course of certain of the hemoglobin diseases, so the reverse is true. Among the 77 pregnancies in 31 women reviewed here, some variation from normal has been seen in both the maternal and fetal prognosis.

Decreased fertility among women with sickle cell anemia has been suspected for many years. Many factors logically are responsible for this condition. Among these are chronic illness, anemia, early demise, and the suggestion that gonadal maturity is delayed. Since most of these obstacles occur frequently in sickle cell anemia, decreased fertility would not be surprising in this condition and is indicated by several findings in our study. Of the 15 adult women with sickle cell anemia (S-S), only 9 ever became pregnant. Among these 9 there was an average of 2.3 pregnancies per patient. In spite of this relatively normal average, less than one-tenth the number of deliveries were performed in women with sickle cell anemia at this hospital during the last 6 years than one would expect among our Negro obstetrical population. In contrast, 16 of the 18 adults studied with sickle cell-hemoglobin C disease became pregnant and the number of deliveries was three-fourths of that expected. Each woman in this group also averaged 2.7 pregnancies. Three of the 5 adults with sickle thalassemia and 3 of the 4 with hemoglobin C disease became pregnant. They averaged 1.7 and 2.7 pregnancies each. Relative infertility among women with sickle cell anemia is strongly suggested by these findings but a hopeful outlook for some is attested by an occasional multipara.

Spontaneous abortion occurred in 19 per cent of pregnancies in patients with sickle cell anemia and 16.3 per cent of those with S-C disease. Only one of the eight pregnancies in hemoglobin C disease ended in abortion and none in the women with sickle thalassemia. These figures are consistent with those given by Anderson in his report. Premature delivery resulted in 29 per cent of the pregnancies associated with sickle cell anemia and in 9.3 per cent of those with S-C disease. These data are summarized in Table II. Fetal survival ranged from 52 per cent in sickle cell anemia to 87 per cent in hemoglobin C disease. Although examination of both the living and the dead offspring has varied in its thoroughness, no persistent fetal defect has been recognized.

TABLE II. FETAL SURVIVAL

TYPE OF HEMOGLOBIN	TOTAL PREGNANCIES	% ABORTION	% PREMATURE DELIVERY	% SURVIVING CHILDREN
S-S	21	19	29	52
S-C	43	16.3	9.3	65.1
C-C	8	12.5	12.5	87.5
S-thalassemia	5	0	0	80.0

Other incidental complications such as toxemia, tuberculosis, and postpartum hemorrhage developed in 5 of the 77 pregnancies reviewed and were essentially uniform in the various groups of women. Abnormal pelvic architecture was noted only once.

Maternal mortality, on the other hand, was interestingly distributed. Four deaths related to pregnancy occurred in the 31 gravidas included in this study (Cases 11, 12, 13, 14). Every one of these women had electrophoretically proved sickle cell-hemoglobin C disease. Not only were they similar in this respect, but each one developed rapidly increasing anemia and bone pain after the sixth month of pregnancy, often followed by recognizable pulmonary infarction. Death occurred during the third pregnancy in 2 cases and in the fifth in another. Another victim had survived a critical period of crisis and infarction during her fifth pregnancy but died with similar symptoms during her next gestation. Three of the women were 26 years of age at

death and the other was 41. The patients with sickle cell-hemoglobin C disease who survived averaged 22 years at the time of their last pregnancy while all those with sickle cell anemia averaged 27 years of age. Thus, out of 16 patients with sickle cell-hemoglobin C disease, 4 died at term after a remarkably uniform sequence of events. Although all of these cases have been previously reported,[2, 7] their clinical courses point out most of the problems encountered during pregnancy in the hemoglobin diseases.

Case Abstracts of Maternal Deaths

G. H., Case 14 (JHH 379041), a 41-year-old Negro woman, registered in the obstetrical clinic in the twenty-fourth week of her third pregnancy in 1957. Both previous pregnancies had ended in spontaneous abortion during the first trimester. The past history revealed only an untreated syphilitic infection. Initial prenatal physical examination was normal. The hematocrit value was 29.5 per cent. The patient continued well until the thirty-fifth week of pregnancy when she began to complain of joint pain which soon involved both forearms and legs. A hematocrit level was 27.5 per cent and blood for hemoglobin electrophoresis was drawn. Two weeks from term she was admitted to the delivery floor complaining of severe constant low back pain. Vital signs were normal and there were no signs of labor but the patient looked very uncomfortable. No other abnormal findings on physical examination were noted. The hematocrit value on admission was 32.5 per cent. Symptoms continued after admission but seemed improved. Twenty hours after arrival the temperature rose and râles and rhonchi appeared in the right lower lung field. Twenty-four hours after admission 1 million units of penicillin was given intramuscularly at a time when the temperature was 102° F. and respirations 24 per minute. At this time the report of the hemoglobin electrophoresis established the diagnosis of sickle cell-hemoglobin C disease. Two hours after administration of the penicillin, shortness of breath, tachycardia, sweating, and slight elevation of the blood pressure were noted. Musical wheezes became generalized over the chest. There was no skin rash or urticaria. The ocular fundi were normal. The hematocrit value was found to be 27 per cent, and the serum bilirubin 2.9 mg. per cent, 1.8 per cent of which was directly reacting. In spite of epinephrine, aminophylline, cortisone, and digitalization, deterioration continued. Moist basilar râles were heard. The patient became disoriented and died one hour later, during which time the fetal heart sounds disappeared. The blood pressure and pulse disappeared and shortly afterward respirations and cardiac action ceased.

Complete postmortem examination (Autopsy No. 27553) revealed widespread infarction and necrosis of bone marrow in the vertebrae, ribs, and sternum. Necrotic bone marrow, including bony spicules, was found microscopically in the major pulmonary arteries and most of their branches, but no macroscopic changes except slight edema were present. The spleen weighed 1,400 grams and was several times normal size with homogeneous maroon parenchyma. Typical lakes of red cells surrounding small follicles were seen microscopically. Other organs, including a term-sized intrauterine fetus, were normal. Fat* could be seen in the necrotic bone marrow and filling many of the pulmonary arterioles and capillaries. Nearly every renal glomerulus contained fat globules in the glomerular tufts and sections of the brain showed the presence of a considerable number of intravascular globules.

H. H., Case 13 (JHH 281428), a 26-year-old Negro woman, developed increasing anemia near term in all 3 of her pregnancies. She had previously been completely well except for fleeting abdominal and joint pain. The third pregnancy was complicated only by varying anemia until 20 days after the expected date of confinement when labor began. Labor did not progress in 5 hours and x-ray pelvimetry showed normal gynecoid architecture. Two hours later pain in both hips developed, apparently unrelated to labor pains. An hour later chest pain began but no râles were heard. The hematocrit value remained about 27 per cent. All symptoms, including those of labor, soon subsided. Labor resumed about 24 hours after

*Fat was identified in the various locations described by the use of frozen sections and staining with either Sudan III or oil red O.

admission and an apparently uncomplicated spontaneous delivery followed 4 hours later. Hemorrhage of about 300 c.c. was attributed to a small vaginal laceration which was repaired. Forty minutes after delivery the patient became unresponsive, with slow respirations and slight fall in blood pressure. Vaginal bleeding increased and the uterus relaxed in spite of bimanual massage. Profound shock and dyspnea developed although blood replacement seemed to be adequate. The hematocrit value at this time was only 19.0 per cent with an icteric index of 50. A subtotal hysterectomy was performed under local anesthesia but death occurred on the operating table 3½ hours after delivery.

At autopsy (Autopsy No. 22596) blood was found in the tracheal tree and intra-alveolar spaces, the source of which could not be determined. There were no gross or microscopic pulmonary emboli of any kind. The spleen was small and scarred and there was hepatomegaly. The pelvic organs were unremarkable save for the the recent subtotal hysterectomy. The S-C electrophoretic pattern was determined by study of the surviving family, of which all three offspring were living and well.

D. J. S., Case 12 (JHH 127304), another 26-year-old Negro woman, was known to have had a sickle cell disease since the age of 4 years. Outstanding in her past history were several episodes of hematuria and transient leg ulcers. Episodes of abdominal and chest pain had occurred but apparently no true hemolytic crises. Her first two pregnancies at the age of 17 had ended in spontaneous abortion. Four years later she developed pre-eclampsia and anemia necessitating transfusions but was spontaneously delivered of a surviving term-sized infant. Her fourth pregnancy ended in the delivery of a premature stillborn infant in the thirty-eighth week of gestation following a crisis characterized by hemolysis and severe bone pain. Within 24 hours overt signs of pulmonary infarction developed. Complete recovery occurred in about 2 weeks. The final pregnancy in 1950 was fairly benign, except for anemia, until the twenty-third week when she was admitted for treatment of a urinary tract infection. Two weeks later aching pain in the forearms, hips, and back began. The hematocrit value at this time was 22 per cent and a single blood transfusion was given. The hematocrit remained about the same and bone pain varied but gradually grew worse over the next 2 weeks. Ten days before the estimated date of confinement pain developed and pulmonary infarction became obvious. Within 8 days she was critically ill. The day before the estimated date of confinement spontaneous delivery of a full-term infant occurred under low spinal anesthesia. Ten minutes later vaginal bleeding began. The second attempt at manual removal of a densely adherent placenta was followed closely by death. It was felt that the blood loss had been adequately replaced.

Autopsy (Autopsy No. 22403) revealed widespread infarction of bone marrow and pulmonary artery emboli. The spleen was small and scarred. No other cause of death was found.

E. F., Case 11 (JHH 305141), a 24-year-old obese Negro woman, had previously been delivered of four full-term viable infants and a stillborn infant. She had not experienced symptoms or hemolysis prior to her fourth pregnancy in 1945 when she was transfused and delivered of a normal term infant with pre-eclampsia the only complication. In 1947, the onset of arm and leg pain and a fall in hematocrit value from 26 to 20 per cent was followed 2 weeks later by the spontaneous delivery of a macerated full-term infant without further maternal complications. In her final pregnancy this patient was not seen in this clinic. During the seventh month she developed aching pains in both thighs and died suddenly within 12 hours at home.

No autopsy was performed. Electrophoresis of the surviving family indicated the presence in this patient of types S and C hemoglobin.

Treatment

The treatment of patients with hemoglobin disease at this hospital has generally followed the suggestions made by Anderson[1] in his paper of 1949. Antenatal care included dietary supplementation, antibiotics when infection

was present, and whole blood transfusions. Therapeutic abortion and cesarean section without obstetrical indications were never used. General, local, and conduction anesthesia have been used without any known detrimental effects. Sterilization was performed on 5 patients with sickle cell anemia and on one with C-C disease but was not done in every case because of the blood disease. Case 20 (S-C) underwent tubal ligation 2 months after a premature delivery at which time she was acutely ill with multiple pulmonary infarctions. She is living and well at the present time. The result of these policies of treatment suggest that some changes may be indicated, particularly in the selection of patients for sterilization.

Comment

Obstetricians have long recognized the importance of anemia during pregnancy and have devoted much time to its understanding. Within the last half century a unique form of anemia, associated with sickling of red blood cells in people of negroid background, has attracted increasing attention. That pregnancy was sometimes unusual in this sickle cell disease was recognized but limitations in accurate diagnostic methods made it impossible to conclude whether or not the prognosis was unusually poor. When these limitations were overcome by practical methods for determining genetic hemoglobin patterns, certain authors recognized that women with some forms of sickle cell disease more often developed complications than with others. This concept has been fortified by other reported data and is the basis for the present study.

Recurrent hemolytic crises with infarction of various organs are typical in sickle cell anemia but are only infrequently seen in the variants thereof. Explanations for the periodic breakdown in erythrocytes containing sickle hemoglobin differ but most investigators believe that it is related to oxygen tension. Infarction may result from primary occlusion of small vessels by tangles of erythrocytes[8] or by embolization of necrotic bone marrow.[7] Most of the other lesions seen in sickle cell disease are probably based on these two processes. For instance, it appears that the underlying mechanism for much of the pain of a crisis is the obstruction of vascular channels by tangles of sickled erythrocytes, resulting in vascular engorgement and distention of the intramedullary cavity of the bones. Some characteristic in the blood of patients with the sickle cell variants prevents hemolysis and sludging of red cells most of the time and may do so throughout life. An interesting observation in the present study was the frequency with which hemolytic and thrombotic tendencies remained completely unrecognized in sickle cell-hemoglobin C disease until pregnancy occurred, but then produced effects at least as devastating as any in sickle cell anemia.

Why erythrocytes containing types S and C hemoglobin should be affected by pregnancy remains a mystery. Lowenstein[9] has demonstrated a significant change in the bone marrow activity of normal pregnant women with a maximum increase of erythropoiesis, and to a lesser extent granulopoiesis, during the third trimester. The fairly sharp rise in hemoglobin production with less increase in the number of erythrocytes just before delivery coincides with the severe complications in S-C disease and may be of significance. From whatever the cause, increasing anemia followed by infarction of both bone marrow and lungs has recurred with such frequency as to demand particular attention when they are seen near term in pregnant women with sickle cell-hemoglobin C disease.

Early pregnancy offers no added problems in the diagnosis of the sickle cell diseases. A typical history and characteristic physical findings are seen in some but in many diagnosis depends upon hemoglobin electrophoresis. Examination of the peripheral blood for sickled erythrocytes remains a useful procedure but is quite unreliable, even in true sickle cell anemia. Jaundice often deepens in sickle cell anemia during pregnancy. Experience in the present series of patients has implied that this is of less significance than a rapidly increasing anemia in persons with previously normal hemoglobin levels. Nearer term, the sudden onset of bone pain and signs of pulmonary infarction may suggest the diagnosis. When these occur it might even be possible to identify fat droplets released from infarcted bone marrow into the circulating blood.[10] Until more specific means of establishing a diagnosis become available, an awareness of the clinical features and catastrophic possibilities is of considerable value.

Although fewer women with sickle cell anemia become pregnant than expected, those who do have developed serious complications less often than the women with sickle cell-hemoglobin C disease. The rather marked increase in both abortions and premature deliveries, particularly in sickle cell anemia, is probably responsible for the decrease in fetal survival since no consistent fetal abnormalities have been noted. This brings up the question of placental infarction. With its sluggish flow of maternal blood and variable oxygen tension, why is this organ not an ideal location for clumping of sickled cells and thrombosis? The high incidence of early parturition suggests this possibility, but neither symptoms nor postpartum examination of placentas has as yet confirmed it. It is possible that the key to the relationship between pregnancy and the sickle cell disease may be found in the placenta.

In the treatment of the hemoglobin diseases during pregnancy, most authors have advocated attention to the antenatal diet with vitamin and iron supplementation, an attempt being made to maintain a hematocrit level of 30 per cent or more. Whole blood has been the most frequent addition to this regime. Although there is no real evidence here that these measures have prevented any of the more serious complications, increasing anemia with resultant decrease in oxygen-carrying capacity may well precipitate the crises near term. Antibiotics are indicated in the presence of infection and have been advocated as a prophylactic measure by some. Anesthesia during delivery or other operative procedures demands optimal oxygenation but otherwise may vary with the anesthetist. Avoidance of trauma, excessive blood loss, and infection during delivery are, of course, always indicated. Mention must be made of anticoagulants, ACTH, oxidants, and acetazoleamide (Diamox). All of these have been given therapeutic trials in sickling crises but none are as yet generally accepted. The occurrence of bone marrow infarction and pulmonary infarction has so often preceded even greater illness that sterilization appears indicated once these complications have developed. In summary, pregnant Negro patients who develop anemia should be thoroughly evaluated and when found to have sickle cell disease, especially sickle cell-hemoglobin C disease, they should be observed and treated with extreme care.

Not any of the observations of this paper are presented as conclusive, for the number of patients is far too small. The obstetrical histories, however, of women with sickle cell anemia have varied so uniformly from those with sickle cell-hemoglobin C disease as to suggest more than chance selection. One group at least became no worse during pregnancy and may even have had fewer symptoms. The other developed increasing symptoms which sometimes preceded death. Many more patients must be carefully studied before these patterns can be confirmed or denied.

Summary and Conclusions

The obstetrical histories of 42 adult Negro women with electrophoretically proved hemoglobin abnormalities have been reviewed. In this group, 31 women with either sickle cell anemia, sickle cell-hemoglobin C disease, sickle thalassemia, or hemoglobin C disease experienced a total of 77 pregnancies with a fetal survival rate exceeding 65 per cent except in sickle cell anemia where only half the pregnancies resulted in living children. While maternal morbidity was greater than normal in many of the patients, it was most marked in those with sickle cell-hemoglobin C disease, and death occurred only in this group.

Some aspects of the pathological processes seen in the sickle cell diseases are discussed with special reference to their occurrence in pregnancy. The realization that these processes may develop for the first time during gestation and may have serious consequences should stimulate diagnosis earlier in pregnancy. Accurate hematological diagnosis, however, depends upon determination of the genetic hemoglobin pattern.

Therapeutic measures have included emphasis on the maintenance of adequate hemoglobin levels by blood transfusions, particularly in those whose hematocrits are usually normal. Besides supporting these measures the present study indicates that once bone marrow and pulmonary infarction have been seen in patients with sickle cell-hemoglobin C disease, future pregnancy carries with it extreme maternal risk.

Briefly, the material reviewed here, supports the suspicion that pregnancy is usually of greater potential hazard to women with sickle cell-hemoglobin C disease than to those with sickle cell anemia, hemoglobin C disease, or other variants thereof. Confirmation of these suspicions awaits further evidence.

Without the encouragement and thoughtful suggestions of such men as Dr. Nicholson J. Eastman, Dr. Ernest W. Smith, and Dr. Arnold R. Rich, this paper would have been impossible.

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THE SICKLE CELL DISEASES IN PREGNANCY

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DURING the past thirty years approximately 140 cases[1-4] of sickle cell disease in pregnancy have been reported in the literature. These case reports have contributed considerably to our knowledge of sickle cell disease in general as well as to our understanding of its effect upon pregnancy. They have served also to stimulate the thinking of obstetricians, internists, and hematologists. The time has now come, however, to evaluate each new case of sickle cell disease with the aid of such newer diagnostic methods as hemoglobin paper electrophoresis and resistance to alkali denaturation.

Hemoglobin analysis by means of paper electrophoresis has made it possible to determine the exact type of hemoglobin with which one is dealing. The different hemoglobins have been designated by letters of the alphabet; e.g., normal adult hemoglobin by A, fetal hemoglobin by F, sickle hemoglobin by S, and other abnormal hemoglobins by C, D, etc. The different combinations of hemoglobins seen in normal individuals and in individuals with various types of sickling are summarized in Table I.

TABLE I. HEMOGLOBINS DETERMINED BY ELECTROPHORESIS

PHENOTYPE	GENOTYPE	HEMOGLOBINS
Normal	AA	A
Sicklemia or sickle cell trait	SA	AS
Sickle cell disease	SS	S-F
Sickle cell-C disease	SC	S-C

Individuals with the sickle cell trait have normal adult hemoglobin (A) and sickle cell hemoglobin (S). Patients with the sickle cell diseases have no adult hemoglobin but have sickle cell hemoglobin (S) plus either fetal hemoglobin (F) or C hemoglobin. Sickle cell disease per se and its variant sickle cell-C disease are inherited hemolytic anemias.

Resistance to alkali denaturation reveals the percentage of fetal hemoglobin. The value of alkali denaturation in the diagnosis of sickle cell disease has not yet been completely exploited as it has been in other hematologic disorders.

The purpose of this paper is to describe briefly methods of diagnosis and management of the sickle cell diseases in pregnancy and to report 6 cases of sickle cell disease and three cases of sickle cell-C disease.

Methods

Since the sickle cell trait or sicklemia occurs in approximately 8 per cent[1] of the American Negro population, and since approximately 90 per cent of our clinic population is American Negro, all patients registering for prenatal care in the Obstetric Out-Patient Department of the Jefferson Medical College Hospital are screened by means of a sickling preparation. The method employed is that of Daland[5] which consists of adding one drop of a 2 per cent sodium metabisulfite solution to a cover slip preparation of peripheral blood. The slide is examined microscopically for the presence of sickle cells in 15 minutes and 30 minutes.

Patients with positive sickling are studied further by means of hemoglobin paper electrophoresis and alkali denaturation. These studies are performed on a single 5 ml. sample of oxalated venous blood. Red blood cells are hemolyzed with distilled water and toluol. One portion of the hemolysate is used for electrophoresis according to the method of Smith and Conley.[6] Electrophoresis separates the types of hemoglobin present; i.e., adult, fetal, sickle, C, etc. The remaining portion of the hemolysate is used for alkali denaturation according to the method of Singer and Chernoff.[7] The percentage of fetal hemoglobin can be determined by measuring the alkali resistant component; this may vary from zero to 22 per cent in sickle cell disease. The percentage of fetal hemoglobin varies in the same individual under different conditions.

Management

Patients with sicklemia are managed in the same manner as those without the sickle cell trait. Patients with the sickle cell diseases are managed conservatively; these patients are seen in the regular Ante-Partum Clinic more frequently than the regular patients, and by the hematologist as well as by the obstetrician. Patients with the sickle cell diseases usually have an excess of iron stores, and iron preparations are not administered unless there is evidence of a coexisting iron-deficiency anemia. These patients are promptly hospitalized at the first sign of any condition that may precipitate a sickle cell crisis; e.g., severe upper respiratory tract infection, pyelitis, cystitis, thrombophlebitis, etc.

During a crisis the patient is treated at bed rest with intravenous fluids as necessary to insure adequate hydration, and with small transfusions of packed red blood cells when the hemoglobin level falls below 7 Gm. per cent. Oxygen is not administered even during labor and delivery unless there is dyspnea or evidence of fetal distress. Labor is not induced nor cesarean section performed because of the presence of sickle cell disease.

Six Cases of Sickle Cell Disease

During 1956 and 1957, 6 cases of sickle cell disease (patients with S-F hemoglobin) were diagnosed. These patients were delivered under the obstetrical and hematological surveillance of the authors. These 6 patients were registered in the Ante-Partum Clinic and consequently were studied by means of routine sickling preparations as well as hemoglobin electrophoresis and alkali denaturation.

The most severe case (E. W. B.) experienced approximately ten crises during her second, third, and fourth pregnancies at the Jefferson Medical College Hospital. This patient was shown to have 100 per cent sickle hemoglobin (zero fetal hemoglobin). Another patient who had experienced several mild crises demonstrated zero fetal hemoglobin on one occasion and 10 per

cent fetal hemoglobin on another occasion. The remaining four patients demonstrated fetal hemoglobin that ranged from 2.3 to 12.9 per cent. It was not possible to demonstrate a correlation between the severity of sickle cell disease and the percentage of fetal hemoglobin.

The oldest patient was a 42-year-old para vi, gravida viii, who was delivered spontaneously of a full-term infant that died at 6 months of age with cerebral palsy. The oldest pregnant patient with sickle cell disease previously reported[8] was 35 years old. A complete summary of the 6 cases of sickle cell disease is presented in Table II.

TABLE II. SIX CASES OF SICKLE CELL DISEASE (S-F HEMOGLOBIN) DURING PREGNANCY

	PATIENT	AGE	GRAVIDITY	PARITY	MATERNAL COMPLICATIONS	FETAL COMPLICATIONS	ALKALI DENATURATION
1.	E. W. B.	33	iv	ii	Icterus Many crises Phlebitis	None	0 % F
2.	S. G.	33	v	iv	Icterus Mild crises Cystitis	None	0 % F 10 % F
3.	M. H.	22	iii	ii	Pneumonia	None	7.1 % F
4.	V. L. K.	42	viii	vi	Icterus Mild toxemia	Cerebral palsy	2.3 % F 12.9 % F
5.	M. F.	32	vi	v	Anemia Triplets	1 stillbirth	10.6 % F
6.	F. L.	29	iv	iii	None	None	3 % F

Three Cases of Sickle Cell-C Disease

Sickle cell-C disease appears to be more serious than sickle cell disease when complicated by pregnancy, according to Smith and Conley.[6] Although we have observed only 3 patients with sickle cell-C disease during pregnancy, we are inclined to agree with Smith and Conley because all 3 of our patients experienced crises. Three of the 6 patients with sickle cell disease never experienced crises. A summary of the 3 cases of sickle cell-C disease is presented in Table III.

TABLE III. THREE CASES OF SICKLE CELL-C DISEASE (S-C HEMOGLOBIN) DURING PREGNANCY

	PATIENT	AGE	GRAVIDITY	PARITY	MATERNAL COMPLICATIONS	FETAL COMPLICATIONS
1.	G. K.	30	vi	v	Slight anemia Mild crises	None
2.	D. H.	25	iii	ii	Anemia Icterus Crises	None
3.	E. G.	37	vi	v	Severe anemia Icterus Crises Stroke	None

Results With the Sickle Cell Diseases

All 9 patients were delivered spontaneously. There were 10 live births and one stillbirth; the weight of the stillborn infant was 1 pound, 14 ounces. There were no neonatal deaths and no maternal deaths.

Comment

The Harlem Hospital workers[2] who reviewed 129 cases of "sickle cell anemia" from the literature and added 9 cases of their own felt that these patients do not live beyond the fourth decade. On the basis of the 9 patients observed and delivered at the Jefferson Medical College Hospital, it appears that with conservative obstetrical management, accurate hematological diagnosis and treatment, and cooperative patients, the life expectancy might very well extend beyond the fourth decade.

It is possible that certain patients previously reported as having "sickle cell anemia," particularly the seriously ill patients, might in reality have had sickle cell-C disease. It is also possible that certain severely anemic patients with positive sickling, previously reported to have "sickle cell anemia," might in reality have had merely sicklemia.

Hemoglobin electrophoresis makes it possible to diagnose differentially sicklemia, sickle cell disease, and sickle cell-C disease.

Summary

1. Prenatal patients are screened for the sickle cell diseases by sickling preparations, followed by hemoglobin electrophoresis and alkali denaturation if sickling is positive.

2. Six patients with sickle cell disease and three with sickle cell-C disease are reported.

3. Patients with sickle cell crises were managed conservatively with intravenous fluids and small blood transfusions as necessary.

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SICKLE CELL–HEMOGLOBIN C DISEASE AND PREGNANCY, INCLUDING A CASE OF OSTEOMYELITIS

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SICKLE cell–hemoglobin C disease, a genetic varient of sickle cell anemia, is usually characterized by mild hemolytic anemia, large numbers of target cells on the peripheral blood smear, and splenomegaly. Occasionally it is asymptomatic; however, severe crises comparable to those occurring in sickle cell anemia have been observed. There are reports that pregnancy increases the degree of hemolytic anemia and precipitates crises.[1] The following deals with a family in whom four females have sickle cell–hemoglobin C disease. They had nineteen pregnancies among them and four crises documented during the pregnancy period. In addition, an unusual complication, acute hematogenous osteomyelitis, followed one of these crises.

CASE 1.—(Index case.) S. K., a 22-year-old gravida ii, para i, was admitted to Philadelphia General Hospital in December, 1957, for generalized bone pain and a foul-smelling vaginal discharge. She had been amenorrheic following her first delivery 5 months previously. One month prior to admission she experienced two episodes of painful swelling of the knees and a thick yellow fluid was aspirated from these joints in another hospital. Five days before admission, after a vaginal douche, she expelled a "large dark clot" without excessive vaginal bleeding. Three days later she developed severe constant bone pain most marked in the lower extremities, hips, and jaws.

A review of her medical records showed two admissions to another hospital in 1949 for pneumonia. In 1950 she was hospitalized 6 months at Philadelphia General Hospital for evaluation of bilateral pleural effusions. Splenomegaly, a hemoglobin of 9.5 Gm. per 100 ml., a positive sickling preparation, and many target cells on the peripheral smear were noted. All studies for acid-fast bacilli were negative. The effusion had the properties of a transudate and its cause was not determined. She had an uncomplicated delivery in July, 1957. Although the hemoglobin while she was in the prenatal clinic was 8.6 Gm. per 100 ml., with a reticulocyte count of 3.1 per cent, the postnatal hemoglobin was 10.1 Gm. per 100 ml.

Physical examination upon admission revealed a thin apprehensive Negro woman who was extremely toxic and dyspneic. The temperature was 102° F., the pulse 120, the respirations 50. The blood pressure was 100 systolic, 60 diastolic. The skin was moist and hot, there were hyperpigmented scars about the ankles resembling old healed ulcers. The conjunctivas were pale and the scleras icteric. Except for pallor, the optic fundi were normal. The respirations were shallow and labored; dullness and diminished breath sounds were present at both bases. The apex beat was at the fifth interspace in the midclavicular line; the rhythm was regular and no murmurs were heard. The liver was not palpable, but a tender spleen was felt 5 cm. below the costal margin. No joint swelling

was noted. Reflexes were hypoactive but equal. The cervix was soft and a foul-smelling brown discharge exuded from a widely dilated os. The uterus was boggy, tender, and enlarged to the size of a 12 weeks' pregnancy.

Urine specimens were of low specific gravity and negative for bile. Examination of the blood revealed a hemoglobin of 6.5 Gm. per 100 ml., a white cell count of 14,800 with 2 per cent metamyelocytes, 65 per cent band forms, 26 per cent segmented neutrophils, 2 per cent monocytes, a reticulocyte count of 0.4 per cent, and many target cells with moderate polychromatophilia and hypochromia on the peripheral smear. Qualitative electrophoretic analysis of the hemoglobin showed an S-C pattern. The blood urea nitrogen, blood sugar, and cholesterol were normal. The sodium was 125 mEq., potassium 3.0 mEq., carbon dioxide 21.2 mEq., and chloride 99.1 mEq. per liter. The total protein was 5.3 Gm., the albumin 2.5 Gm., and the globulin 2.8 Gm. per 100 ml. The cephalin flocculation was 2 plus, the thymol turbidity 3.0 units and the thymol flocculation was 1 plus. The alkaline phosphatase was 2.3 Bodansky units. The direct bilirubin was 3.1 mg. and the total bilirubin 5.3 mg. per 100 ml. The first strength tuberculin test gave a 2 plus reaction. Several blood and urine cultures were sterile. On the fifth hospital day, a beta Enterococcus resistant to penicillin and tetracycline but sensitive to chloramphenicol was grown from the cervical culture. Febrile agglutinins for *Brucella abortus,* Proteus OX-19, Salmonella somatic antigens A, B, C, D, E, and flagellar antigens b, c were negative. X-ray films of the chest showed bibasilar pneumonitis and a left pleuropneumonic process. The heart was normal in size. The electrocardiogram showed a sinus tachycardia.

The patient was treated with narcotics, large quantities of fluids, alkali, blood, and antibiotics. She remained febrile and toxic through the fifth day at which time the hemoglobin was 8.6 Gm. per 100 ml., the white cell count 14,800 with a shift to the left, and the reticulocyte count 5.4 per cent. The direct bilirubin determination of 1.1 mg. and the total bilirubin of 3.1 mg. per 100 ml. gradually fell to normal values by the eighth day. X-ray views of the lumbar spine, pelvis, and femurs showed minimal osteoporosis with a slight increase in trabecular markings. There was no biconcaving of the intervertebral discs. Many nonspecific small rounded radiolucent areas were noted in the distal femurs, patellas, and acetabula. A linear irregular density in the proximal right tibia was thought to be residual of previous bone infarction. The skull was normal. The spleen was enlarged.

The patient improved and was ambulatory on the eighth day though still having occasional febrile episodes. Pelvic examination was not remarkable. Repeat hepatic function studies showed no significant changes. On the eleventh day she complained of right shoulder pain, but physical and roentgenographic examinations were normal. Five days later she passed placental tissue accompanied by profuse vaginal bleeding which required several blood transfusions and an emergency dilatation and evacuation. Her postoperative recovery was satisfactory. Upon discharge 2 weeks later, the spleen could no longer be palpated and the hemoglobin was 8.7 Gm. per 100 ml. with a reticulocyte count of 3.4 per cent.

She returned to the hospital 4 weeks after this discharge because of a hot tender lump in the left arm of 2 days' duration.

The temperature was 100.5° F. The mass was superficial, hot, tender, and fluctuant; it measured 6 cm. by 6 cm. and overlay the anterior border of the left deltoid muscle. The spleen was not palpable.

On two Fishberg concentration tests the specific gravity of the urine was 1.012 and 1.015. The hemoglobin was 9.3 Gm. per 100 ml. and the white cell count 8,600 with a normal differential. Febrile agglutinins were again negative. X-ray views of the long bones revealed similar pathologic processes in the proximal diaphyses of both femurs, the left humerus, and the mid-diaphysis of the right humerus. There were very large irregular medullary lesions associated with periosteal reaction most marked in the femurs (Fig. 1). The periosteal reaction, which gave an appearance of layering, extended the length of the medullary component. A soft tissue swelling was noted overlying the left humerus. The mandibular films revealed minimal osteoporosis with increase in trabeculation especially between the teeth.

TABLE I. CLINICAL FINDINGS IN A FAMILY WITH S-C DISEASE

	PATIENT AND CASE NO.								
	S. K.-1	B. K.-2	J. K.-3	W. K.-4	S. R-5	L. H.-6	G. W.-7	B. A.-8	Q. T.-9
Age (years)	22	58	died at 39	37	32	28.9	28.0	26	24
Relation to case 1		Father	Mother	Brother	Sister	Sister	Sister	Sister	Sister
Hemoglobin pattern	S-C	A-S	?	?	S-C	S-C	S-C	A-C	A-C
Joint and bone pain	+++	0	0	0	0	+	+++	0	0
Hydroarthrosis	Yes	0	0	0	0	0	Yes	0	0
Abdominal pain	0	0		0	0	0	0	0	0
Hematuria	0	0		0	0	Yes	0	0	0
Pleural effusion	Yes	0	0	0	0	0	Yes	0	0
Splenomegaly between crises	0	+		0	++++	0	+	0	0
Splenomegaly during crises	+++					+	++		
Pregnancies	G. ii P. i		G. viii P. viii		G. iv P. iv	G. v P. v	G. viii P. vi	G. iii P. iii	G. v P. v
Crises related to pregnancies	1				0	1	2	0	0
Crises unrelated to pregnancies	0	0			0	0	1	0	0

She was treated with chloramphenicol and became afebrile on the fifth hospital day though she continued to have mild migratory bone pain. Purulent-appearing material aspirated from the soft tissue mass on the ninth and tenth days failed to grow bacteria, acid-fast bacilli, or fungi. One month later a roentgenographic bone survey showed little change in the skeletal lesions. A definite radiolucent horizontal communication between the medullary lesion and the periosteal reaction was noted in the left humerus (Fig. 2). She was discharged and given 4 weeks of tetracycline therapy at home. She felt well and the superficial mass in the left arm regressed. Repeat x-ray films of the long bones compared to those taken 2½ months before showed no significant change.

CASE 5.—S. R., a 32-year-old gravida iv, para iv, female sibling with marked splenomegaly has been completely asymptomatic.

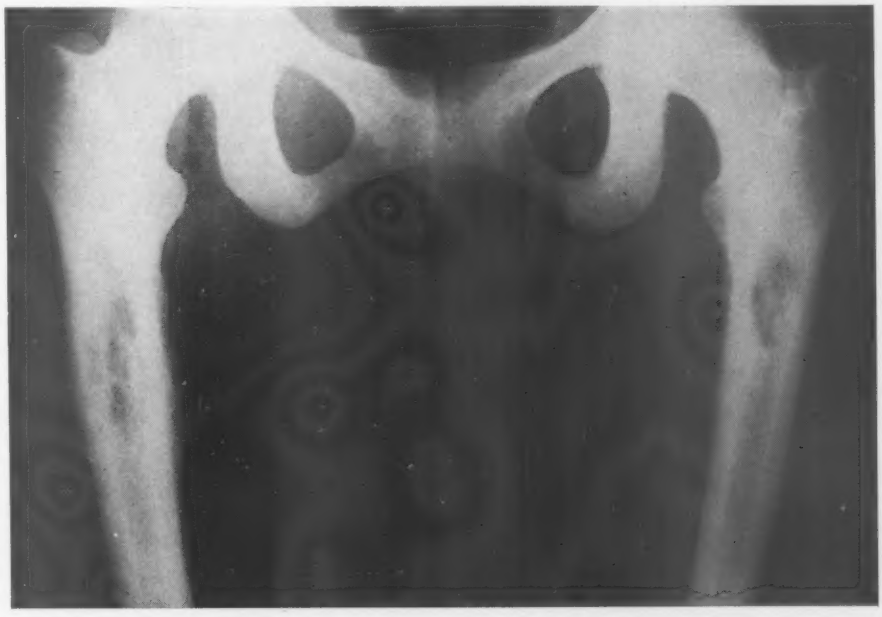

Fig. 1.—Patient S. K. Osteomyelitis. Irregular destructive medullary processes with surrounding periosteal proliferation in proximal femurs bilaterally.

CASE 6.—L. H., a 28-year-old gravida v, para v, female sibling, stated that she had had infrequent episodes of joint pain since childhood. She had been admitted to the maternity service of Philadelphia General Hospital for deliveries in 1947, 1950, 1951, 1952, and 1954. These deliveries and the puerperium were normal. The hemoglobin determinations ranged from 9.3 to 11.0 Gm. per 100 ml.

During the fourth month of her second pregnancy, she had an episode of painless hematuria of 2 days' duration. One month later she was admitted to the prenatal service because of hematuria associated with right flank pain. The temperature was 102° F.; the tip of the spleen was palpated and conjunctival petechiae were present. Numerous sickled red cells were observed in the urinary sediment. Aeruginosa type species was cultured from the urine. The hemoglobin ranged from 8.4 to 9.2 Gm. per 100 ml., the reticulocyte count was 5.4 per cent, and bilirubin was normal. The diagnosis was thought to be sickle cell crisis with renal infarction. She improved on conservative treatment and was discharged in 10 days.

CASE 7.—G. W., a 28-year-old gravida viii, para vi, female sibling, stated that she had had frequent attacks of bone pain as well as pain and swelling in the knees which frequently required aspiration. She had been admitted twice to Philadelphia General Hospital; in 1951, in sickle cell crisis and in 1955 for pneumonia.

TABLE II. LABORATORY FINDINGS IN A FAMILY WITH S-C DISEASE

	PATIENT AND CASE NO.					
	S. K.-1	B. K.-2	S. R.-5	L. H.-6	G. W.-7	Q. T.-9
Hemoglobin A		48%				56%
Hemoglobin S	Present	52%†	51%	52%	48%	
Hemoglobin C	Present		49%	48%	52%	44%
Alkali resistant hemoglobin (F)		1.2%	0.5%	1.6%	1.0%	
Ferro hemoglobin solubility		44%	40%	42%	40%	90%
Hemoglobin*	6.7-12.4	14.6	9.5-11.6	8.4-12.5	7.0-11.6	13.7
Target cells	+++	0	++++	++	++++	+
Bilirubin	0.8-5.3	0.1	0.9	0.4-0.9	0.7-2.1	1.0
Cephalin flocculation	2+	0	0	0	0	0
Thymol turbidity	3.0	0.9	3.6	5.1	4.6	4.2
Thymol flocculation	1+	0	2+	3+	3+	3+
Total Protein	5.3	6.6	6.8	6.0	6.8	6.8
Albumin	2.5	3.1	3.4	2.2	3.3	3.0
Globulin	2.8	3.5	3.4	3.8	3.5	3.8
α_1Globulin		0.41	0.28	0.45	0.34	0.31
α_2Globulin		0.53	0.42	0.48	0.44	0.48
βGlobulin		0.72	0.66	0.80	0.61	0.82
γGlobulin		1.87	2.06	2.05	2.06	2.15

*W. K., Case 4, had a hemoglobin of 15.0-15.5; B. A., Case 8, had a hemoglobin of 13.3 and an A-C pattern.

†An A trail on paper electrophoresis was present.

In 1951 she was seen with severe knee pain and paresthesias of the hands and feet. The tip of the spleen was palpated. The hemoglobin was 12 Gm. per 100 ml. and the bilirubin ranged from 1.3 to 1.8 mg. per 100 ml. X-ray films of the skull, chest, vertebrae, pelvis, and long bones were within normal limits.

In 1956 she was admitted to another hospital for dilatation and evacuation of an incomplete abortion. Following this procedure she developed severe generalized bone pain and required several blood transfusions. She developed hepatomegaly, splenomegaly, and a left pleural effusion during the course of the crisis.

She was followed in the prenatal clinic of another hospital during her last pregnancy in 1957. The prenatal hemoglobin determinations ranged from 8.8 to 11.0 Gm. per 100 ml. and the hemoglobin on admission was 10.5 Gm. per 100 ml. Although the

Fig. 2.—Patient S. K. Osteomyelitis. Irregular destructive medullary process with minimal surrounding periosteal proliferation in proximal left humerus. Note radiolucent horizontal intracortical tract.

delivery was normal, she developed fever, icterus, and splenic and slight hepatic enlargement on the third postpartum day. The hemoglobin dropped to 7.7 Gm. per 100 ml. and remained at that level for 5 days despite several transfusions. Examination of the bone marrow showed erythroid hyperplasia. No foci of infection were found. She eventually improved and was discharged 2 weeks later.

Sickle Cell–Hemoglobin C Disease

In Tables I, II, and III are summarized the clinical, laboratory, and x-ray findings in the family we have studied. In general these are in accord with observations of others.[1, 7]

TABLE III. X-RAY FINDINGS IN A FAMILY WITH S-C DISEASE

	PATIENT AND CASE NO.						
	S. K.-1	B. K.-2	S. R.-5	L. H.-6	G. W.-7	B. A.-8	Q. T.-9
Hemoglobin pattern	S-C	A-S	S-C	S-C	S-C	A-C	A-C
Heart	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Spleen	Enlarged	Normal	Enlarged	Enlarged	Normal	Normal	Normal
Skull	Normal		Normal	Normal	Normal	Normal	Normal
Vertebrae	Slight osteoporosis and increased trabeculation	Normal	Normal	Normal	Slight osteoporosis and increased trabeculation	Normal	Normal
Pelvis	Slight osteoporosis and increased trabeculation		Normal	Normal	Slight osteoporosis and increased trabeculation	Normal	Normal
Long Bones	Bone infarction, proximal right tibia (acute osteomyelitis, complication)	Bone infarctions, distal femurs		Bone infarctions distal femurs	Bone infarctions distal femurs		Cortical thickening, distal femurs

The incidence of sickle cell anemia and sickle cell–hemoglobin C disease in American Negroes is approximately the same. One patient with sickle cell–hemoglobin C disease was found in a survey of 500 randomly selected Negro clinic patients.[2] A normal body habitus is observed in contrast to the leg-trunk disproportion usually seen in patients with sickle cell anemia. A high incidence of vitreous hemorrhages and/or retinopathies has been reported in sickle cell–hemoglobin C disease.[3, 4] A case of pulmonary infarction has been observed.[5] The heart is not enlarged in uncomplicated cases. Mild hepatic dysfunction is usually present. In addition to slight elevations of cephalin flocculation and thymol turbidity described by others,[6, 7] we found an elevation in gamma globulin. Sickle cell–hemoglobin C disease may be a cause of hematuria.[8] Joint and bone pain, both during and between crises, may be quite distressing and hydrarthrosis is fairly common. The roentgenographic changes in the bone are caused primarily by thrombotic episodes which result in bone infarctions. Aseptic necrosis of bone may be produced, particularly in the capital femoral epiphysis.[1]

In contrast to sickle cell anemia where splenomegaly is found in only 10 per cent of adults,[9] over 50 per cent of adult patients with sickle cell–hemoglobin C disease have splenomegaly. However, as Smith and Conley[1] have emphasized, there is no good correlation between age, severity of disease, and degree of enlargement of the spleen in sickle cell–hemoglobin C disease. Small fibrotic spleens may be present. A crisis may result in a transient increase in the size of an already enlarged spleen or the first recognition of its enlargement.

Pregnancy

Smith and Conley[1] reported upon 5 pregnant patients with sickle cell–hemoglobin C disease who, in every instance, showed marked increase in hemolytic anemia often associated with other manifestations of crisis during the last trimester. Three of these patients were symptom free prior to their pregnancies and a fourth was asymptomatic during the preceding 12 years. Edington[7] described several cases of sudden death in pregnant women with sickle cell–hemoglobin C disease.

To compare the frequency of crises during pregnancy of sickle cell anemia with sickle cell–hemoglobin C disease, the protocols of cases of sickle cell anemia associated with pregnancy previously reported were examined. None were proved by electrophoresis. In 1955, Eisenstein, Posner, and Friedman[10] reviewed 286 of these cases and included, among others, those of Fouché and Switzer[11] who had collected 23 cases of sickle cell crisis associated with pregnancy prior to 1949. An examination of the cases reviewed by Eisenstein and co-workers from 1949 to 1955[12-22] revealed 20 more cases of crisis. Therefore, the incidence of crises in 286 pregnancies was approximately 43 (15 per cent). However, in 10 of these pregnancies with 7 crises,[13, 17, 21-25] mild anemia or splenomegaly was present, findings more compatible with sickle cell–hemoglobin C disease. In the family reported, only 4 crises occurred in a total of 19 pregnancies (21 per cent). Although this incidence is not greatly different from that in sickle cell anemia, nevertheless only one crisis in this family occurred outside pregnancy.

Osteomyelitis

Chronic osteomyelitis complicating sickle cell–hemoglobin C disease has recently been reported.[26] In our patient, S. K., acute hematogenous osteomyelitis followed a sickle cell crisis which in turn complicated an incomplete

abortion. Unfortunately, cultures from an overlying soft tissue abscess failed to grow a causative organism, nor did serologic tests indicate a Salmonella infection, although the Salmonella species most frequently produce osteomyelitis in patients with sickle cell anemia.[27, 28] The patient's relatively good clinical condition, in spite of the extensive bone destruction, was due, we think, to intensive antibiotic therapy.

Our observations indicate that the radiologic picture of acute osteomyelitis complicating sickle cell–hemoglobin C disease is similar to that reported for sickle cell anemia.[29] There is multiple diaphyseal involvement by irregular destructive medullary processes associated with periosteal proliferation and intracortical fissuring (Figs. 1 and 2). The medullary process does not cross the epiphyseal line. The periosteal reaction is limited to the extent of the medullary destruction. A short intraosseous sinus tract may connect the medullary and cortical reaction (Fig. 2).

Summary

The clinical, laboratory, and roentgenographic characteristics of a family in whom four adult females had sickle cell–hemoglobin C disease are described. In a total of 19 pregnancies, 4 crises occurred, an incidence approximating that reported for sickle cell anemia. It is suggested that patients with sickle cell–hemoglobin C disease are no more prone to crises during pregnancy than patients with sickle cell anemia. However, crises during pregnancies may be the only times when the sickle cell–hemoglobin C disease is symptomatic.

The first case of acute osteomyelitis complicating sickle cell–hemoglobin C disease in pregnancy is reported.

Drs. F. Ginsburg, Chief of Obstetrics, C. Thompson, Chief of Medicine, and J. Shapiro, Resident in Obstetrics, aided us in the management of these cases. C. A. J. Goldberg performed the hemoglobin analyses. L. Wodicka, S. Lulias, and V. S. Sheffer performed the laboratory studies.

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Gynecology

THE OVARIAN SEROUS CYSTADENOFIBROMA

A Report of 25 Cases

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THE serous cystadenofibroma is a relatively rare tumor of the ovary which, in general, has not been accorded a deserved clear-cut pathologic status apart from related ovarian lesions. The tumor was described by Wolfe[18] and by Frankl[5] in 1927. It has usually been regarded in these and scattered subsequent references as a neoplasm lacking in hormonal activity, although abnormal uterine bleeding was not uncommonly observed in patients with this tumor.[6, 9, 12] In 14 reported cases of serous adenofibroma and cystadenofibroma of the ovary, Scott found 6 associated with leiomyomatous uteri and in 5 others a recorded history of abnormal uterine bleeding.[11] The bleeding was ascribed, respectively, to endometrial polyps, leiomyomas of the uterus, adenocarcinoma of the endometrium, endometrial hyperplasia, and adenocarcinoma of the endometrium, abnormalities not thought at that time to be indicative of endocrine dysfunction.

The serous cystadenofibroma may now be regarded at least in its formative stages as a localized or general region of ovarian stromal hyperplasia mingled with germinal inclusion cysts, rather than as a genuinely autonomous neoplasm. Ovarian cortical stromal hyperplasia and its equivalent, the polycystic ovaries of younger women, are now believed to be productive sources of estrogen.[15] Estrogen-secreting properties have also been ascribed to some Krukenberg and Brenner tumors which may involve a supportive reactive hyperplasia of ovarian cortical stroma.[1, 17] Recent studies relating to serous cystadenofibroma of the ovary call attention to the frequently associated menstrual abnormalities, and suggest a similar functional role.[2, 4, 10]

Prompted by this consideration, a series of serous cystadenofibromas available from the surgical and autopsy files of the Massachusetts Memorial, New England Deaconess, and Pondville Hospitals were investigated in order to disclose the presence or absence of the stigmas of estrogenic activity in related organs. It was also hoped that further information might be gleaned regarding the pathogenesis of this entity and its specific status in the schemata of ovarian tumors.

Observations

The clinical charts, surgical and autopsy protocols, and the available pathologic material from 25 cases of ovarian serous cystadenofibroma were analyzed. The average age of the patient was 57 years. The youngest patient was 34 and the oldest 82.

The incidence of obesity, hypertension, and diabetes mellitus approximated that of the usual hospital population. Hypertension was recorded in 8 instances, obesity 3 times, and diabetes twice.

Eight patients gave a history of sterility or miscarriages. Twelve patients complained of abnormal vaginal bleeding. In all save one instance the bleeding could be ascribed to polyps, fibroids, uterine cancer, or other associated pathologic conditions. Uterine fibroids were found in 11 cases, endometrial polyps in 6, and endometrial hyperplasia in 7. There were 4 instances each of endometrial and mammary carcinomas in this series. Other abnormalities are listed in Table I.

TABLE I. PATHOLOGIC CONDITIONS ASSOCIATED WITH 25 CYSTADENOFIBROMAS

Ovary.—	
Cortical stromal hyperplasia	7
Serous cystadenocarcinoma of the ovary	1
Intracystic papillary serous cystadenoma	1
Ovarian fibroma	1
Struma ovarii	1
Dermoid cyst of ovary	1
Uterus.—	
Leiomyoma of the uterus	11
Endometrial hyperplasia	7
Endometrial polyp	6
Adenocarcinoma, endometrium	4
Endometriosis	2
Carcinosarcoma of uterus	1
Carcinoma of cervix	1
Carcinoma in situ of cervix	1
Adenomyosis	1
Leiomyosarcoma	1
Others.—	
Mammary cancer	4

Endometrial curettings or vaginal smears suitable for analysis were available in 16 cases. Atrophic endometrium was found in 5 instances while in 11 cases evidence of excess estrogen activity was present. This was shown by hyperplastic endometrium in 7 cases while the remainder showed proliferative or secretory endometrium or the presence of cervical or vaginal estrogen effect.

Serous cystadenofibroma was the principal pathologic finding in 7 of the 25 patients. Their ages ranged from 44 to 69, averaging 54 years. Three patients complained of menorrhagia or postmenopausal spotting, one of multiple miscarriages, one of pain in the lower abdomen, and 2 of painless enlargement of the abdomen.

Fig. 3.

Fig. 2.

Fig. 1.

Fig. 1.—Germinal epithelium invaginates between coarse papillomatous projections of the cortical stroma. (×90.)
Fig. 2.—Epithelial downgrowth is observed in areas of cortical stromal hyperplasia. (×40.)
Fig. 3.—Whorled, plump, darkly staining stromal cells indicate ovarian cortical stromal hyperplasia. (×545.)

The ovarian tumors were most often relatively large in this group, weighing up to 220 grams and measuring up to 11.5 cm. in greatest diameter. The cystadenofibroma was bilateral in 2 cases.

Three patients gave a history of past pelvic operation for (1) fibroids and endometrial hyperplasia and polyps, (2) a papillary cystadenoma of low-grade malignancy of the opposite ovary, and (3) fibroids.

Incidental pathologic findings in the 4 other patients were fibroids in one case, endometrial polyps and cystic endometrium, with cortical stromal hyperplasia and a fibroma of the opposite ovary in the second, cystic dysplasia of endometrium in the third, and in the fourth instance cortical stromal hyperplasia of the opposite ovary.

The 18 other cystadenofibromas were viewed as casual incidental findings. Of the total series, 15 were under 3.5 cm. in diameter, while 10 exceeded this dimension.

In the group in which the cystadenofibromas were incidental findings, one patient had a serous cystadenocarcinoma of the opposite ovary, one an intracystic papillary serous cystadenoma arising within the cystadenofibroma, and two others a dermoid cyst and a struma ovarii, respectively, of the opposite ovary.

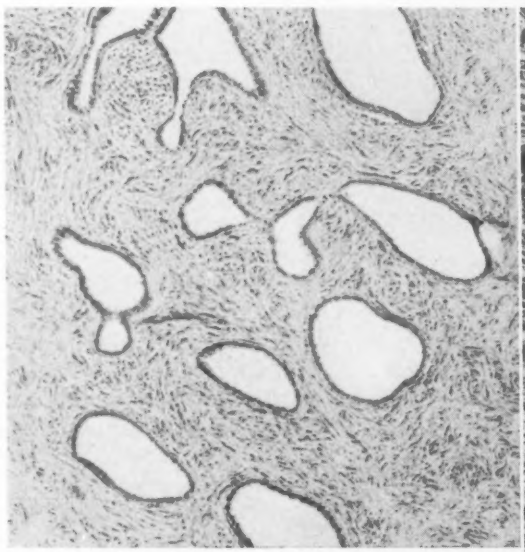

Fig. 4.

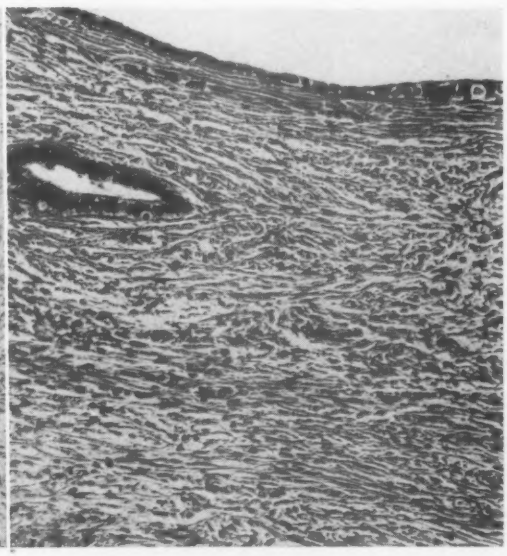

Fig. 5.

Fig. 4.—Tiny cystic cavities are rounded or retain their tubular shape. (×40.)
Fig. 5.—Cells which line cysts may be columnar, cuboidal, or flattened. (×90.)

The gross appearance of the cystadenofibroma varied according to the relative preponderance of cystic and solid components of the tumor. It was usually a firm, gray, glistening mass, the surface of which was lobulated or convoluted. Blood vessels coursed over the surface of the larger specimens and thin-walled cysts of variable size, filled with clear fluid, protruded externally. At times, the smooth contour of the surface or of the lining of the larger cysts was broken by pitting or by sessile surface papillomas. The cystadenofibroma may occur as a pedunculated growth from the surface of the ovary. The cut surface revealed in cystic portions of the tumor a honeycombing of multiple smooth-walled cysts usually a few millimeters in diameter, which contained a watery fluid. These cysts were smoothly lined and assumed tubular or branching contours.

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 6.—Well-differentiated columnar cells with centrally placed nuclei have clearly defined basement membranes. (×90.)
Fig. 7.—Lining cells of a cystadenofibroma may resemble those of a Fallopian tube. (×545.)
Fig. 8.—A "burnt-out" cystadenofibroma shows flattened germinal cells and a hyalinized stroma. (×545.)

Microscopically, under low power, the cystadenofibroma appeared to have its origin in tubular invaginations of flattened germinal epithelium, often between coarse papillomatous projections of the cortical stroma (Fig. 1). The tubular ingrowth of epithelium frequently occurred in areas of stromal hyperplasia (Fig. 2). This change is demonstrated under higher power by the presence of a whorled pattern of large, plump, darkly staining stromal cells containing fusiform nuclei with distinct chromatin aggregates (Fig. 3). Occluded glandlike ingrowths of germinal epithelium formed tiny cystic spaces lined by a single payer of flattened, cuboidal, or columnar epithelium. The cysts may retain their tubular character or present as smooth, round cavities (Figs. 4 and 5). Calcified psammoma bodies were occasionally in evidence and thecomatosis was sometimes seen.

The lining cells of the cysts were frequently cuboidal or columnar, often ciliated, and contained oval, centrally placed nuclei oriented to the long axes of the cells. A clearly defined basement membrane was noted (Fig. 6). These cells may closely simulate the lining cells of the Fallopian tube (Fig. 7).

In the "burnt-out" cystadenofibroma, the cells which lined the cystic cavities were more frequently flattened and the intervening stroma suggested an ovarian fibroma. Stromal cells were pink with dark, spindle-shaped nuclei. Areas of calcification were here frequent and often hyalinization was present (Fig. 8).

Comment

The cystadenofibroma is regarded as developing from germinal inclusion cysts in areas of local or general ovarian cortical stromal hyperplasia. Its frequent association with uterine stigmas of excess estrogen stimulation and with a variety of the pathologic conditions of the female genital tract that at present are believed to be related to an excess of estrogenic hormone suggest that this growth may have the same proclivity for endocrine activity as ovarian cortical stromal hyperplasia, at least in its earlier stages of development.

There is now strong evidence to implicate a prolonged period of hyperestrinism as a conditioning or causative factor in the genesis of endometrial hyperplasia and leiomyomas of the uterus. It is believed that these disorders are reflections of a polyglandular endocrine imbalance associated on the morphologic plane with pituitary basophil hyperplasia and ovarian cortical stromal hyperplasia with inferred hypersecretion of FSH and estrogenic substances. The hyperplastic endometrium, due to an initial prolonged phase of hyperestrinism, is the substrate upon which secondary endocrine abnormalities may act to induce endometrial carcinoma.[3, 13, 14]

Endometrial cancer and its precursors have been induced by exogenous estrogen in the rabbit and in the human. The disease is believed by some authors to have a significantly higher frequency in women with feminizing ovarian mesenchymomas than in the general population.[7, 8]

The present series was of necessity a selected one. In 18 of 25 patients, the cystadenofibroma was clinically and pathologically relegated to secondary importance. The tumor was itself responsible for hospital treatment in only 7 patients. The prominence of associated endocrine-dependent disease is nevertheless of interest and lends support to the probability that the cystadenofibroma is capable of secreting estrogen. It is noted that 4 patients had breast cancer, another a tumor in which hyperestrinism plays a role.[15]

The serous cystadenofibroma appears to be closely related to germinal inclusion cysts, taking its origin from tubular downgrowth of these cells into hyperplastic ovarian cortical stroma. It is a benign growth, hyperplastic rather than truly neoplastic, at least in its formative phase. The presence of an

intracystic papillary cystadenoma within the structure of a cystadenofibroma, and the involvement of a serous cystadenocarcinoma of the contralateral ovary, once by past history and once concurrently, attest to a relationship between the cystadenofibroma and the papillary serous cystadenomatous tumors. Germinal epithelial derivatives thus retain their capacity for diverse and metaplastic differentiation.

Summary

Twenty-five cases of serous cystadenofibroma, 7 of which constituted the major clinical and pathologic finding, are reported. In 11 cases there were associated uterine abnormalities partly ascribable to estrogen effects.

The lesion consists basically, at least in its early phase of development, of germinal inclusion cysts in an ovary that is the seat of localized ovarian cortical stromal hyperplasia.

It is suggested but not proved that at some phase of development these tumors possess estrogen-secreting properties.

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PRIMARY ARGENTAFFIN CARCINOMA (CARCINOID) ARISING IN AN OVARIAN TERATOMA

A Report of 2 Cases

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SINCE 1933, the pathology department of the Charity Hospital of Louisiana at New Orleans has examined approximately 1,500 ovarian tumors excluding tuboovarian abscess masses. In reviewing the ovarian tumors, we found 2 cases of an extremely rare malignant tumor arising in an ovarian teratoma. This tumor has an affinity for silver staining and therefore is called an argentaffinoma or carcinoid tumor.

According to Wolfe,[22] the term carcinoid was first coined by Oberndorfer[14] in 1907 and was meant to indicate a specific tumor of the intestinal tract, as the tumor is derived from Kultschitsky[9] (granular) cells lying in the crypts of Lieberkühn. Although the histological characteristics were malignant, the tumor seemingly followed a benign clinical course. This was a mistaken concept, as it was soon apparent that in spite of their slow growth and localization, carcinoid tumors in general ultimately become invasive and produce both local and distant metastases. Fortunately, these malignant tumors are rarely fatal.

Because of the low-grade malignancy the tumor became known as an argentaffin carcinoma.[1, 5] The most common site of origin of argentaffin (carcinoid) tumors[15] is in the region of the ileocecal valve, but the tumor may be found in other portions of the gastrointestinal tract. All of the primary argentaffin (carcinoid) carcinomas of the ovary are associated with ovarian teratomas. This is readily understandable, for segments of the intestinal tract are often reproduced in these neoplasms.

Review of the Literature

In 1939, the first 2 recorded cases of an argentaffin (carcinoid) carcinoma occurring in the wall of an ovarian teratoma were reported by Stewart, Willis, and de Saram.[20] Only an occasional case has appeared in the literature since that time. Singular cases have been reported by Gabrilove[6] in 1941, Hartz[7] in 1945, Blackwell and Dockerty[1] in 1946, Mitchell and Diamond[13] in 1949, Hughedson[8] in 1955, Falkmer[5] in 1956, and another isolated case by Martin and associates[12] in 1956. The derivation of the primary argentaffin elements in the ovary varies from gastric and intestinal epithelium[6, 7, 12, 20] to a bronchial-

respiratory epithelial origin,[1, 3, 5, 13] while in some cases the origin is not identifiable.[8] Because of the histological characteristics of a teratoma, an argentaffin carcinoma can develop, though it is extremely rare in the male reproductive organs. A case of an argentaffin carcinoma arising in a testicular teratoma has been reported by Simon and co-workers.[19] It is conceivable that an argentaffin (carcinoid) tumor can metastasize to an ovary and Wolfe[22] presents such a case.

One of our 2 cases had its origin in the intestinal tract, but the origin of the other could not be ascertained. We have reviewed 9 similar cases of primary argentaffin carcinoma arising in ovarian teratomas. Adding our 2 cases brings the authentically reported total to 11 cases.

Because of the rarity of a primary argentaffin carcinoma arising in the female generative tract we are presenting the following cases.

CASE 1.—M. H. (C.H. No. T44-127480), a 51-year-old Negro woman, has been followed in the medical clinics of this Charity Hospital since 1944. Her presenting complaints were hot flushes, dizziness, and weakness since the menopause 8 years before. The diagnosis of "menopausal syndrome" was made and the patient was started on estrone in weekly injections of 10,000 units intramuscularly. She was next seen on May 27, 1948, with the complaints of nervousness, palpitations, and anorexia. The same regime of estrone weekly injections was ordered. This form of medication continued for 9 weeks and on July 20, 1948, the patient began having moderate to severe headaches in the parietal area, neck pain, nervousness, palpitations, and vague dull pain in the right lower quadrant of the abdomen. Three days later, on July 23, 1948, she had an acute onset of vaginal bleeding which she estimated to be approximately half of a cupful. After this she continued spotting for the following 2 days. She was referred from the medicine clinic to the gynecology clinic for evaluation of the postmenopausal bleeding.

Physical Examination.—The patient did not appear acutely or chronically ill. Her weight was 110 pounds, blood pressure 158/100, pulse 80 and regular, and the oral temperature normal. The respirations were even and regular at 20 per minute. The pelvic examination was described as normal with the exception of a cystic left ovary enlarged 2 to 3 times. Blood chemistry examinations were normal and the Kline test was positive. The electrocardiogram showed left ventricular hypertrophy and ventricular premature beats. The initial impression was postmenopausal bleeding with the etiology as estrogenic response. The diagnosis of malignancy of the uterine fundus or ovary was considered.

Operative Course.—On Aug. 9, 1948, the patient was given a general anesthetic of ether and ethylene and a dilatation and curettage was performed with a scanty return of endometrial material. After the abdomen was prepared, a left paramedian abdominal incision was made and the abdomen was opened in layers. Examination of the pelvic organs revealed a cystic left ovary measuring approximately 6 cm. and a slightly enlarged solid right ovary. Examination of the abdominal cavity was entirely within normal limits. No further pelvic lesions were found and a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful and the patient was discharged to the clinic for follow-up care and evaluation. She has continued to have hypertension, vertigo, and tinnitus. She is now approximately 10 years post operation and repeated bowel surveys reveal multiple diverticulae of the colon. No lesions of the small bowel have been found.

Description of the Specimen.—Received in a damp cloth was a previously opened uterus with the cervix attached. The left tube and ovary and the right tube and ovary were also attached. The left ovary had been previously opened. The left ovary measured 5 by 4.3 cm. The right ovary measured 4 by 2 cm. The myometrium was 1.3 cm. thick. The left ovary contained numerous bright yellow nodules varying in size from 0.3 to 1 cm. in diameter. On cut sections these nodules were filled with bright yellow semisolid material. Sections were submitted for microscopic study.

Final Pathologic Diagnosis.—(Slide No. 48-7204.)

1. Dermoid cyst of the left ovary with infiltration of the contents into the ovarian stroma and granulomatous reaction. Among the numerous tissue elements was a carcinoid (argentaffin) tumor (Fig. 1) such as is seen in the intestinal tract.

2. Minute fragments of endometrial stroma with several atrophic glands.

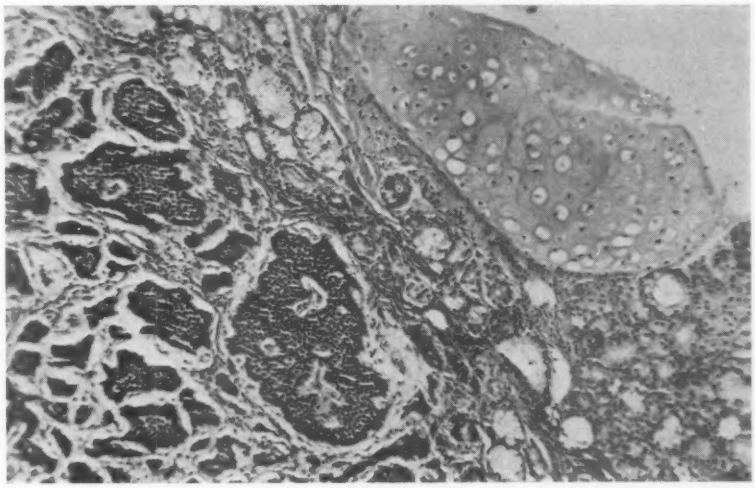

Fig. 1.—Case 1. Argentaffin carcinoma (carcinoid) in ovarian teratoma showing cartilaginous elements (×100).

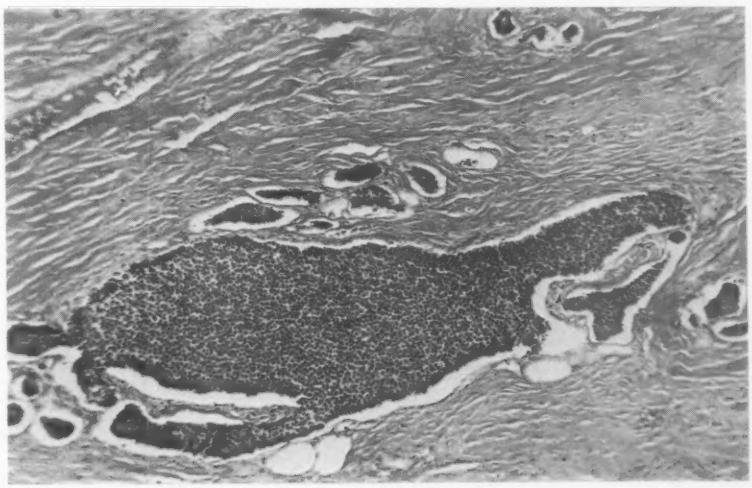

Fig. 2.—Case 2. Argentaffin carcinoma (carcinoid) arising in ovarian stroma (×100).

CASE 2.—A. A. (C.H. No. L56-242492), a 56-year-old Negro woman inmate of the East Louisiana State (mental) Hospital, was first seen in the Charity Hospital in New Orleans on Dec. 20, 1956, after an acute episode of severe generalized abdominal pain which was associated with profuse sweating, a shocklike state. The attendant accompanying the patient was unable to supply further information except that the patient had been vomiting for about 6 hours and the pain was concentrated in the region of the umbilicus. The patient had been given antibiotics and analgesics and her usual dosage of chlorpromazine hydrochloride* (100 mg. three times each day) for hebephrenic schizophrenia. No catamenic or obstetrical history was obtainable.

*Thorazine, Smith Kline & French Laboratories, Philadelphia 1, Pa.

Physical Examination.—The patient presented herself in acute abdominal pain, sweating profusely, and feeling cold and clammy. The blood pressure was 200/120, pulse 108, and the rectal temperature was 101°F. The abdomen was distended and rigid and no bowel sounds were audible. The pelvis was described as impossible to examine bimanually but there was a firm, bulging mass in the cul-de-sac which was quite tender. A flat plate of the abdomen revealed gas in the large bowel but no free gas under the diaphragm. The diagnosis of an acute abdominal crisis was made and a ruptured tuboovarian abcess was considered likely. She was immediately placed on the emergency operating schedule.

Operative Course.—The patient was given a satisfactory general anesthetic of ether and ethylene and the abdomen was prepared for surgery. A left paramedian incision was made and the abdomen was opened in layers. Inspection of the pelvic organs revealed a ruptured 20 cm. left ovarian cyst grossly appearing to be a dermoid. There was a large amount of sebaceous-appearing material free in the peritoneal cavity with obvious origin from the ruptured left ovarian cyst. The remainder of the pelvic organs and the other ovary were considered normal. The patient received 500 ml. of whole blood during the surgical procedure, which consisted of a bilateral salpingo-oophorectomy and appendectomy. Further elective surgery was postponed because of the numerous other surgical emergencies. Thirteen uneventful postoperative days later (following the pathology diagnosis) she was given another general anesthetic and a total abdominal hysterectomy was performed. She was discharged on Jan. 12, 1957, on the seventh uneventful postoperative day. The hypertension has persisted. There have been no symptoms of recurrence of the malignancy, approximately eighteen months after the operation.

Description of the Specimen.—Received in formalin was a large mass consisting of a previously opened cystic structure attached to a multinodular mass. The cyst on reconstruction measured 10 by 10 cm. The outer wall of the cyst was roughened, with fibrous tags running from it. The inner lining of the cyst was roughened with multiple white plaques arranged in a tree-bark-like appearance. At the base of the cyst there was a nodular elevation measuring 3.5 by 3 cm., white in appearance, with in one end a pigmented papillomatous appearance. On cut section, the cystic structure was identified within the attached solid mass measuring 13 by 9 by 7 cm. which appeared well encapsulated, and which had been previously bisected. The cut surface showed numerous areas of cystic degeneration. The solid portion of the tumor had a yellowish-tan appearance and was firm in consistency. There were areas of hemorrhage and necrosis scattered throughout the solid portion. No areas of calcification or cartilage were identified.

Final Pathologic Diagnosis.—(Slide No. 56-19130.)

1. Acute and chronic periappendicitis.

2. Brenner tumor of the right ovary.

3. Teratoma of the left ovary, with predominantly argentaffinoma elements; (Fig. 2) probably malignant.

Comment

Several authors[2, 3, 11] have reported that cystic teratomas constitute 15 to 20 per cent of all ovarian tumors. Primary malignancy arising in cystic teratomas is rarely encountered, about 1.5 per cent according to Marchetti,[11] despite the presence of embryonic structures in this neoplasm. Argentaffin carcinoma arising in a cystic teratoma is an uncommon neoplasm, but it is probably more frequently encountered than the reported cases in the literature would lead one to believe. The tumor's malignant characteristics make it important that these growths should be reported. Pearson and Fitzgerald,[18] in their review of 140 argentaffin carcinomas, described the features of this type of tumor that affirm its malignant characteristics.

Thorson and his associates,[21] discussed at length several cases that came under their care and presented the syndrome of skin flushing and right-sided cardiac involvement. This "carcinoid syndrome" is believed to be due to the liberation of excessive amounts of serotonin.[21] Erspamer[4] was the first to assume that the enterochromaffin cells of the gastrointestinal tract contained and liberated a substance which he called "enteramine" (5-hydroxytryptamine). Page[16] in 1952 and Lembeck[10] in 1953, by laboratory experimentation with serotonin, were able to reproduce some of the findings of Erspamer,[4] and demonstrated that this substance had a specific action on smooth muscles of the blood vessels which contributed to the "flushing" attacks that have been described by clinical investigators.

Recently Page[17] has discussed the biochemical nature of serotonin and points out that its end product, 5-hydroxyindoleacetic acid, is eliminated from the body by the kidneys. It may well be that this substance, when found in excessive amounts in the urine, could establish a diagnosis of a malignancy that would otherwise be missed.

Thorson[21] observed that about 20 per cent of the carcinoids of the small intestine metastasized and in the female the ovary is a common site of this metastasis. Olson and Gray[15] point out the importance of removing the involved tissue and the local lesion when a diagnosis of argentaffin carcinoma is made. The tumor grows slowly and excision of the primary lesion may diminish the symptoms of the "carcinoid syndrome" even when there is metastatic extension.[15]

Most of the carcinoids are seen by general surgeons who do intestinal surgery; however, the possibility of a carcinoid—and its malignant character—must be kept in mind. Cystic teratoma occurs bilaterally in 20 per cent of the cases.[2] When a cystic teratoma is present in one ovary, wedge resection of the opposite ovary is indicated.

In one of the cases reported in this paper operation was performed 10 years ago and there was no evidence of recurrence on the patient's last visit in September, 1957. The other patient came under the care of this hospital so recently that it is too early to evaluate any long-term involvement. We hope that the presentation of these 2 cases will re-emphasize the occurrence of these malignant tumors in teratomas of the ovary.

Summary and Conclusions

Two additional cases of primary argentaffin carcinoma (carcinoid) arising in an ovarian teratoma have been presented. A review of cases that have been reported in medical literature is included, and the "carcinoid syndrome" and the malignant nature of these tumors has been re-emphasized.

We wish to extend personal thanks to Dr. Adolph Jacobs, Chief of the Independent Unit, and to Dr. Herman Cohen, for their encouragement and helpful guidance in the preparation of this paper.

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A VERY LARGE BRENNER TUMOR

With Comments on Certain Points in Histogenesis

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(From Camborne-Redruth Hospital)

MOST Brenner tumors are of small dimensions, are without manifestation of hormonal activity, and are frequently found only incidentally at operation or autopsy. Occasionally, however, an ovarian neoplasm of this type may reach very large proportions. This is already evident from Brenner's original paper,[3] in which he recorded a tumor almost "as large as a man's head" in a 62-year-old woman. Giles,[4] at a meeting of the Royal Society of Medicine, reported on an ovarian growth weighing 8.2 kilograms, which was, most probably, a Brenner tumor. Unfortunately no illustrations are available, but the history of a large abdominal mass for 16 years in a 60-year-old woman, causing mechanical symptoms only, and the microscopical data are in accordance with such an assumption. Reel and Foster[6] recorded a Brenner tumor measuring 28 by 14 by 25 cm. and weighing 5.8 kilograms in a 64-year-old Negro woman, and Neimann[5] reported one measuring 25 by 18 by 10 cm. and weighing 6.8 kilograms in a 45-year-old multiparous Negro woman. While this paper was in preparation Averbach and associates[1] described an ovarian mass, in a 70-year-old woman, which weighed 8.7 kilograms and which they regarded as a Brenner tumor. However, the photomicrograph reproduced in their paper, our study of a section kindly sent us by Dr. Averbach, and the subsequent correspondence leave some doubt in our minds as to the validity of their diagnosis.

These outsize Brenner tumors do not lend themselves to histogenetic study, and as the histogenesis is still in dispute we shall make no attempt to discuss the various theories so far advanced. It is worth stressing, however, that it is the epithelial element of which the origin is uncertain. There appears to be increasing agreement that the thecomatous fibrous stroma, which is an integral part of the growth, is derived from ovarian mesenchyme and that it differs in no way from the stroma of a pure thecoma with its intracellular lipids, or from the thecomatous areas of a granulosa cell tumor. Indeed, it may well be that the hormonal activity of the latter is, at least in part, dependent on the amount and productive activity of its thecomatous component. The same appears to be true of the Brenner tumor, as an increasing

number of cases of this rare ovarian neoplasm have now been published[2] where the tumor was associated with endometrial hyperplasia and uterine bleeding. Both thecomas and Brenner tumors may become so fibrotic that they can no longer be separated from ovarian fibromas, and with increasing fibrosis, to which Brenner tumors are particularly prone, hormone production may be considerably or entirely suppressed.

Fig. 1.

Fig. 2.

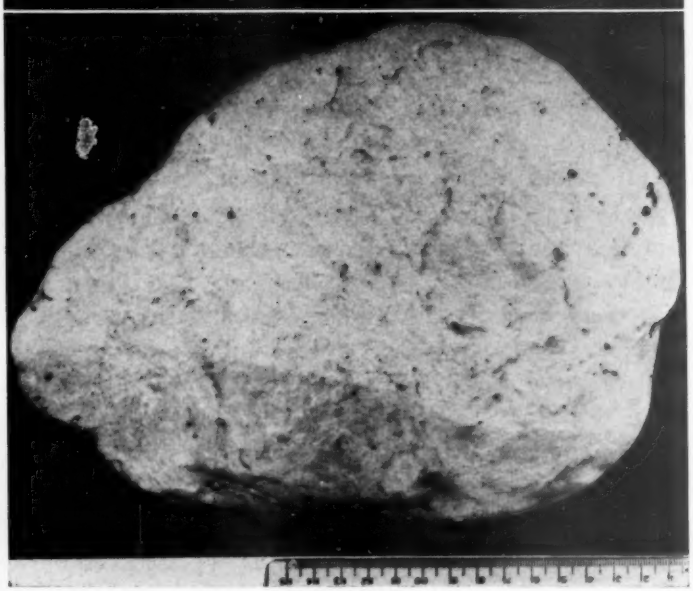

Fig. 1.—Bisected specimen. Outer aspect.
Fig. 2.—Bisected specimen. Cut surface.

The fact that Brenner tumors occur comparatively frequently in combination with other primary ovarian growths, especially pseudomucinous cystadenomas, is probably not without significance. According to some authors, including ourselves, it underlines the retained plasticity of the ovarian stroma which, by a process of dedifferentiation, may regain some of its pluripotential

properties and develop simultaneously in different directions, resulting in a combination of tumors. We would emphasize, however, that we regard the derivation of the epithelial nests as an unsolved problem.

The Brenner tumor is one of the rarest of primary ovarian neoplasms. In our own limited material the incidence was 1 in 332 ovarian tumors of all types. Among this number we encountered 2 granulosa cell tumors and 12 thecomas. Brenner tumors occur more frequently after the menopause than before, grow slowly, are confined to the gonad, and are usually unilateral, benign, and small. A most striking feature of the outsize Brenner tumors has

Fig. 3.

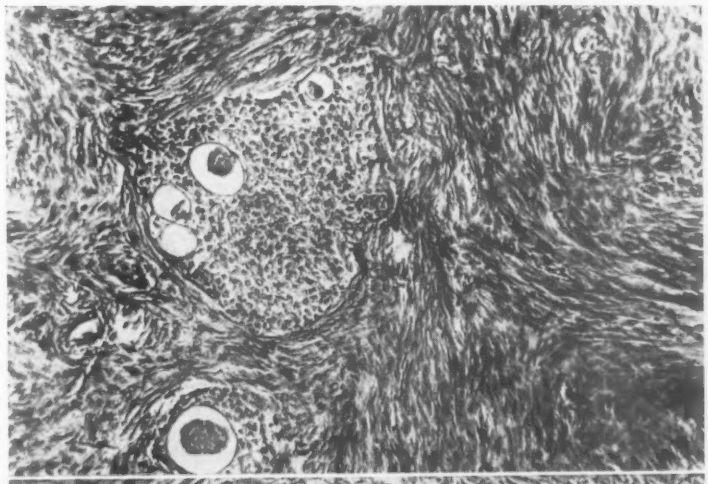

Fig. 4.

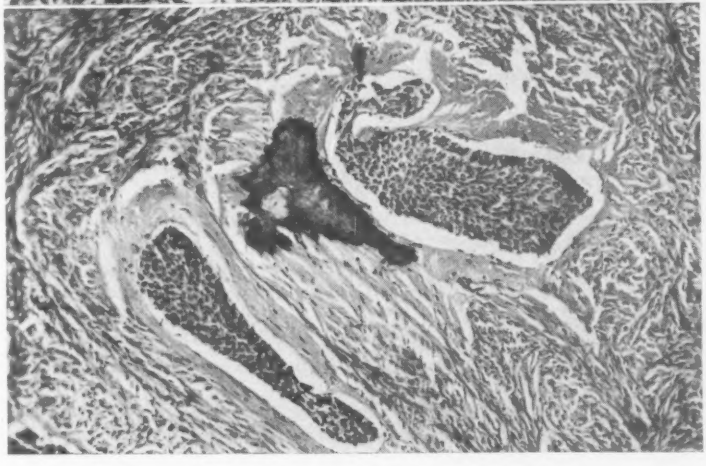

Fig. 3.—Epithelial islets surrounded by thecomatous stroma. (×70.)
Fig. 4.—Hyalinization and calcification around epithelial nests. (×70.)

been the absence of major subjective complaints. There may be a feeling of abdominal weight, some degree of dyspnea, and ankle edema, but on the whole, in view of their size, they produce little discomfort. Ours is a case in point.

Case Report

The patient, a 63-year-old single woman, was referred to one of us (J. G. H. I.) complaining of shortness of breath for 5 years, which had become more troublesome for the preceding 2 years, during which time she had become aware of abdominal enlargement. The menstrual history was without note. Menstruation had commenced at the age of 12 years, the cycle had been regular every 28 days, lasting 5 days, and the menopause had occurred at the age of 53.

On examination she was found to be hypertensive with a blood pressure recording of 210/100. There was edema of both ankles and lower legs up to the knees and a large, hard, mobile mass was filling most of the abdomen up to the costal margins. Hematological examination showed her to be anemic with a hemoglobin of 60 per cent. A diagnosis of large ovarian tumor was made and was confirmed at laparotomy. The mass proved to be an enlarged right ovary and a right oophorectomy was performed without difficulties on July 3, 1957. The patient made an uneventful recovery and was discharged after 17 days. She was seen again on Oct. 28, 1957. She was feeling well at this time and had no symptoms beyond some slight swelling of the right leg.

Macroscopical Description.—The mass was ovoid in shape, encapsulated, with a smooth though knobby outer surface. It measured 28 by 25 by 18 cm. and weighed 8.7 kilograms (Fig. 1). At one aspect 12 cm. of a stretched, distal part of a Fallopian tube was attached. The tumor was extremely hard, cut with great difficulty, and gave a gritty sensation suggestive of focal calcification. The cut surfaces were very firm in consistency, grayish in color, and of a whorled or feathery structure similar to that of fibroma (Fig. 2) but also displaying streaks or areas of a yellowish hue.

Microscopical Description.—The growth was surrounded by a dense fibrous capsule and possessed much fibrous stroma. Cellular parts were made up of plump fibroblasts arranged in bundles or fanlike, alternated with hyalinized areas. These contained scattered calcified areas. This fibrous stroma incorporated many epithelial islets of varying shape and size and irregular distribution (Figs. 3 and 4). They were made up of regular, uniform epithelial cells with oval nuclei and a moderate rim of eosinophilic or poorly staining cytoplasm. Many of these masses were solid and here the epithelium was occasionally of stratified appearance, but some displayed one or more small, frequently central acini containing structureless eosinophil material. Special stains showed much, occasionally very dense, reticulum throughout, PAS-positive, diastase-resistant material in the acinar lumina, and very fine, similar droplets within the tumor epithelium, but no glycogen was demonstrable. In frozen sections there were a few lipid-rich areas within the stroma, usually in the more hyaline areas and hence, presumably, due to degeneration, but no anisotropic crystalline lipoids were seen with polarized light. A few coarse lipid droplets were present in the epithelial cytoplasm. These features are typical of a Brenner tumor.

Summary

A very large Brenner tumor, which weighed 8.7 kilograms, is described. To our knowledge this is the greatest size so far observed. Its structure was typical; it was hormonally inactive and had produced little discomfort in spite of its size. Some of the features of Brenner tumors are discussed.

We are grateful to Professor R. A. Willis for reading the manuscript and to Miss Phyllis E. Coleman for help with the photography.

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DEPARTMENT OF CURRENT OPINION

Clinical Problems

MUMPS DURING PREGNANCY

Case Presentation

A 25-year-old married, white woman, gravida iv, para iii, who had had one abortion, was first seen when 6 weeks pregnant. In the eighth week she experienced fever, pain, and swelling of both parotid glands, which kept her in bed for one week. She had been exposed to mumps as had her children, 2 of whom also developed the disease. While ill, the patient began to spot vaginally. This stopped after 4 days and her pregnancy continued normally.

Problem: The question posed by this inquiry is whether the virus of mumps can cross the placenta and, if so, can anomalies or other pathologic lesions of the fetus result? A specific question is also asked: Can mumps acquired in the early stages of gestation cause abortion?

Consultation

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Mumps during pregnancy is a rare occurrence and there are few articles on the subject in the world literature. Rubella has been much studied but in regard to epidemic parotitis (mumps) there is much less material. Bowers[1] in 1953 summarized the subject and added 2 cases, bringing the total to 84 cases reported since 1849. Since 1953, only 3 more articles[2, 3, 4] on this subject have been published. A resurvey of the literature discloses that 129 cases have been reported; of these, 25 were associated with congenital defects of various types and severity, and 10 with abortion or stillbirth. This latter figure is hard to assess since the rate corresponds to that found normally. In specific cases, however, such as Bowers', the evidence is certainly suggestive that mumps may cause abortion.

The incidence of defects varies from one observer to another depending upon the method of classification, the severity, and the thoroughness of examination and follow-up. In 7 of the 25 cases, the original report was not available; in another 7, the mumps occurred after the fourth month and could hardly

have been responsible for congenital abnormalities reported. Of the remaining 11 cases, one was chorioretinitis diagnosed at the age of 1½ years. The mother had had mumps at 16 weeks of pregnancy and the baby had had chickenpox at the age of 3 months. One was a hypospadius, which is a relatively minor defect. One infant was a mongoloid and the mother had had mumps during the fourth month. The mother was 42 years old and the toxoplasmosis skin test on the baby was positive (any one or more factors may have been operating here).

So, of the total of 130 cases (129 previously reported plus my case, above), 6 per cent of the infants were born with anomalies which might have been the result of mumps. This is a considerably lower percentage than reported by Bowers[1] (14 per cent) and Dumont[2] (30 per cent) for the first 3 months. There is a tendency to under-report the normal babies delivered of mothers who had mumps during the gestation. This exaggerates the risk as determined by a study of the literature.

The problem can be attacked in another way by studying large numbers of congenitally abnormal babies and determining the occurrence of mumps (or other virus diseases) during the corresponding pregnancies. Kay[5] in 1953 surveyed 273 defective children and found only 7 whose mothers had had virus diseases during pregnancy (one case of mumps). Dogramaci and Green[6] in 1947 studied 434 cases of congenital heart disease and found only 9 cases of virus infections in the mothers (one of mumps). However, it has been documented that viruses can cross the placenta; cases of smallpox, chickenpox, measles (rubeola), and poliomyelitis have been reported in the newborn following infection of the mother shortly before delivery.

To evaluate accurately the risk of mumps to the fetus, an epidemiologic approach would be necessary, using modern statistical methods in large series of cases. As with rubella, the percentage of reported abnormalities appears to be decreasing as the number of reported cases increases.

It is probable that mumps during early pregnancy may cause malformations of the fetus but, because available evidence is scanty and inadequate, the exact degree of risk is uncertain. The same holds true for abortion.

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The questions raised do present problems. The spotting described does not mean that the pregnancy will be lost or that the fetus is damaged. Mumps is so seldom encountered in the adult that concrete evidence is difficult to assess. The fact that this 25-year-old patient did have fever, pain, and swelling of both parotid glands in a time sequence would be compatible with the entity of an epidemic parotitis. The vaginal spotting occurred at a theoretical time as a projected cycle date. Had this individual been free of illness at the time spotting occurred there would have been concern only on the basis of

threatened abortion. Most infections attacking the fetus do not cause immediate abortions. The fact that the mumps virus infrequently does cause orchitis or oophoritis supplies evidence of viremia. There is controversy on the possibility of the mumps virus crossing the placental tissue. The viruses of smallpox, chickenpox, and influenza, and certain bacteria do spread to the fetus.

Siegel and Greenberg[1] found that, of 1,064 reportable diseases, mumps occurred in only 24 gravid patients (an incidence of less than 0.2 per cent). Anomalies were not found nor was spontaneous abortion observed. Greenhill[2] quotes Bowers to the extent that mumps may cause abortion as well as abnormalities. Greenhill quotes Wallgren[2] and also Grönvall and Selander[2] as more pessimistic. On this basis it might be assumed that the mumps virus could conceivably cross the barrier. With the infrequency of the disease and the improbability of spread to the fetus it would seem that there was little likelihood of vaginal bleeding resulting from fetal insult.

With respect to the question of resultant anomaly, one would have to admit the theoretical possibility but, of all the complications, illnesses, and accidents which occur during any one pregnancy, it is more of a surprise that injuries to the fetus occur so infrequently. Even so, some doubt or mistrust may remain in the mind of the individual, but one would be hard pressed to present evidence or logic to defend the position that the fetus had had any anomaly resulting from epidemic parotitis.

The management would then logically be unaltered on a statistical basis in spite of the possible parotitis in pregnancy.

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Editor's Comment

One of the consultants mentioned that the solution to this problem could be best obtained by an epidemiologic study utilizing statistical methods, and this is certainly true. However, the number of cases is so small that considerable time will be required to complete such a study. A start along this line has already been made by Siegel and Greenberg[1] who gave an initial report on virus diseases in pregnancy and their effect on the fetus. Such a well-planned study as theirs will add a great deal to our knowledge and it may provide a specific answer to the problem of mumps occurring during the early stage of gestation.

There does not seem to be much evidence to substantiate the thought that mumps, as such, can produce abortion.

A follow-up of this specific patient was obtained from the obstetrician who presented the case. The patient was delivered of a normal 8 pound, 3 ounce, boy at term. The pediatric consultant found no abnormalities of the child on physical and x-ray examination. Skin testing of the mother and the baby was performed using mumps skin test antigen. In 24 hours the mother had a strong positive reaction (indicating immunity) while the baby showed no reaction at all.

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INCOMPETENT INTERNAL CERVICAL OS

Case Presentation

Mrs. L. S., aged 27 years, gave the following obstetric history: She had no living children although she had been pregnant on 4 occasions. Each of the pregnancies had terminated spontaneously between the fifth and seventh months. The first and third terminated in a more or less usual manner with the onset of bleeding and pains and progression to delivery. The second and the fourth, however, differed. During the second pregnancy, at the end of the sixth month, without pain or bleeding, the bag of waters was suddenly extruded through the introitus. The patient pushed the bag into the vagina with her fingers. The next day labor began followed by rupture of the membranes and rapid progression to delivery. The fourth pregnancy terminated at the seventh month. The bag of waters descended to the introitus and ruptured. Labor began shortly thereafter. The delivery was normal but the infant did not survive.

This patient is now pregnant for the fifth time and according to the menstrual history she is in the fourteenth week.

Vaginal examination revealed that the uterus contained a pregnancy and was compatible in size to that indicated by the history. The cervix was soft and short and admitted 2 fingers. The adnexa were normal. The pelvis was adequate. A cytosmear for cancer was negative.

Problem: What should be the management of this patient who is now pregnant for the fifth time?

Consultation

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The patient presented in this clinical problem would appear to have true incompetence of the cervix. The fact that she has had 4 pregnancies and yet has no living children is highly significant. That 2 of those pregnancies terminated between the sixteenth and twenty-eighth weeks of gestation without pain and bleeding is of even more significance. It would appear that the internal os of the cervix had proved to be mechanically incapable of containing the enlarging products of conception. The history in 2 of the abortions of a watery discharge from the vagina, of a sense of pressure in the vagina due to the prolapsed membranes, and of the absence of pain or bleeding prior to rupture of the membranes certainly suggests the diagnosis of cervical incompetence.

It is unusual that the patient did not have a history of some operative procedure such as a dilatation and curettage prior to the first gestation, or following the first abortion, as this entity does not usually seem to be congenital. Recently, however, there has been some evidence that cervical incompetence may be inherited.

Even in the presence of a known history of previous cervical incompetence it would be somewhat unusual for the patient's cervix to be effaced

and dilated as early as the fourteenth week because the products of conception at that early date usually are not of such magnitude as to efface and dilate the cervix. It is conceivable, however, that a condition such as presented by this patient could exist.

The management of this patient during the fifth gestation would include a Shirodkar type of cervix closure in an effort to prevent another middle trimester abortion. The operation has been found by both Dr. Shirodkar[1] and by us[2] to be carried out most effectively around the fourteenth to sixteenth weeks of gestation, before the cervix becomes too effaced and dilated.

The operation consists of placing a Dacron ligature of Mersilene, 5 mm. in width, under the vaginal mucosa and completely encircling the cervix. The ligature is placed under the vaginal mucosa by means of special ligature carriers. It is securely anchored to the underlying fascia of the anterior cervix after the bladder has been reflected upward. The ligature is then pulled snugly around the entire cervix and sutured together and to the fascia in the posterior aspect of the cervix.

Following the operation the patient is kept in bed for a week or 10 days. She is maintained on small oral doses of one of the newer progesterone derivatives and on one of the vitamin C hesperidin preparations. Upon returning home the patient is limited to moderate activity, but she is not required to stay at bed rest.

Delivery is best carried out by cesarean section at 38 or 39 weeks of gestation so that the encircling ligature will not be disturbed. In that manner the patient may have more than one pregnancy after a successful closure of the cervix.

Closure of the cervix is no panacea for all types of habitual abortions. It must be used only in the presence of proved incompetence of the cervix. Predisposing to not one, but to 2 operations, its indications must be strictly adhered to if more good than harm is to be the ultimate result.

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A. F. Lash, M.D., Chicago, Ill.,
Clinical Professor of Obstetrics and Gynecology, University of Illinois School of Medicine

The diagnosis based on the history and findings would be an incompetent internal os of the cervix of either congenital or traumatic origin. Unfortunately, at this time, with the patient already in the fourteenth week of pregnancy, no further diagnostic measures may be carried out. Although, obviously, an incompetent internal os of the cervix is present, one cannot say whether or not an anomaly or hypoplasia of the uterus may also be present.

Therefore, since 2 fingers can be introduced into the cervix, this abnormal patency of the cervix must be corrected by either multiple purse-string sutures of fascia, of braided silk, or of nylon at the level of the junction of the cervix and corpus according to the technique of Shirodkar. If preferred, several catgut sutures may be placed to plicate the thinned-out area of defect sufficiently to narrow the canal at the internal os. The purse-string suture is placed beneath the mucosa by a large aneurysm needle suture carrier. This is cautiously

used in order not to tear any of the uterine or cervical arterial branches. Perforation or laceration of vessels has been known to occur with resulting hemorrhage or hematoma formation.

If the uterus begins to contract postoperatively and reaches a crescendo of violent contractions, the sutures must be severed or rupture of the uterus may occur. (There have been 3 instances of rupture above the level of the sutures.) If the bag ruptures, the condition is irremedial and the termination of the pregnancy may be encouraged. Following the expulsion of the placenta, the defect in the circumference of the corporocervical region can usually be determined and is found either anteriorly or laterally. The area may be excised in an oval, wedge-shaped form and the wound closed with 2 or 3 layers of catgut interrupted sutures of No. 2 chromic catgut.[1, 2] Postoperatively, antibiotics should be administered prophylactically because the cervix may contain bacteria that can become pathogenic in a fresh wound.

History of repeated or habitual abortions (i.e., 3 or more) is not sufficient evidence for the diagnosis of an incompetent internal os of the cervix. Only on the physical findings of the abnormally dilated internal os, as described in the above case report, can the diagnosis be made. Patients have been observed who give a history typical of an incompetent cervical os but who possess no demonstrable defect at the internal os. These have responded favorably to the weekly administration of large doses (500 mg.) of Delalutin, particularly if the pregnandiol levels were below normal. Also, instances of a combination of etiological factors such as hypoplasia of the uterus, septate uterus, or a submucous fibroid with or without incompetency of the internal os must be appreciated because the correction of one factor does not eliminate the other.

Endocrine factors must play a part, for incompetent placentation has been observed wherein the pregnancy was retained to term but the fetus died 2 or more weeks before term and a small fibrotic placenta was found. The occurrence of premature labor 5 and 6 weeks after an apparently successful repair must be explained on an endocrine basis or by ascending infection from the cervix into the decidua, resulting in an intrapartum infection and termination of the pregnancy.

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1. Lash, A. F., and Lash, S. H.: Am. J. Obst. & Gynec. 59: 68, 1950.
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Editor's Comment

Both consultants have indicated that this condition may occur subsequent to traumatic injury of the cervix and that it may be on a congenital basis, but one of them does not think that the latter is a very frequent cause. While the etiology remains somewhat obscure, it is apparent that in some patients an incompetence of the internal os does exist and that surgical correction may contain the fetus within the uterus until term or near term.

Both consultants have stressed that this type of surgical procedure is not a cure-all for all repeated or habitual abortions and that it should be performed only in those cases in which the diagnosis of incompetent cervix has been proved. It is not without hazard. Labor may start and progress so rapidly that pending rupture of the uterus may occur before there is time to cut the constricting suture material.

I am not certain that the ideal suture material has yet been obtained.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

SELECTED ABSTRACTS

Journal of Clinical Endocrinology and Metabolism

Vol. 18, November, 1958.

*McArthur, J. W., Worcester, J., and Ingersoll, F. M.: Urinary Excretion of ICSH and FSH Activity During the Normal Menstrual Cycle, p. 1186.

*McArthur, J. W., Ingersoll, F. M., and Worcester, J.: Urinary Excretion of ICSH and FSH Activity by Women With Disease of the Reproductive System, p. 1202.

*Sandberg, H., Paulsen, C. A., Leach, R. B., and Maddock, W. O.: Estrogen Excretion in Ovariectomized Women Receiving ACTH, p. 1268.

McArthur, Worcester, and Ingersoll: Urinary Excretion of ICSH and FSH Activity During the Normal Menstrual Cycle, p. 1186.

The changes in the day-to-day excretion of ICSH were determined qualitatively throughout 17 menstrual cycles in 13 normal adult women. This was done by evaluation of the repair of ventral prostatic atrophy in hypophysectomized immature male rats. The changes in FSH excretion were determined by changes in the testicular weight.

It was concluded that the normal menstrual cycle is characterized by: (1) a midcycle peak period of FSH and ICSH excretion, during the early phase of which there is a change in the ratio of ICSH to FSH and a transient preponderance of ICSH (the onset of the midcycle peak is closely related in time to the shift in basal body temperature); (2) a late luteal trough followed by a rising trend in the excretion of both hormones beginning toward the end of the luteal phase and continuing into menstruation.

J. EDWARD HALL

McArthur, Ingersoll, and Worcester: Urinary Excretion of ICSH and FSH Activity by Women With Disease of the Reproductive System, p. 1202.

The method for determining the activity of ICSH and FSH excretion was the same as employed by the authors in the investigation of normal menstruating women.

In this study, 11 women were investigated. Clinically they suffered from dysfunctional bleeding, Stein-Leventhal syndrome, psychogenic amenorrhea, hypopituitarism, and rudimentary ovaries.

*These articles have been abstracted.

The results indicate definite differences between these patients and normally menstruating women with respect to the excretion levels of both ICSH and FSH. The fluctuations were variable with no definite pattern. In 6 patients there was a suggestion of lowering of ICSH relative to FSH excretion.

J. EDWARD HALL

Sandberg, Paulsen, Leach, and Maddock: Estrogen Excretion in Ovariectomized Women Receiving ACTH, p. 1268.

Nine women from whom the ovaries had been removed, varying in age from 35 to 52 years, were studied for urinary estrogen excretion following the administration of ACTH. The ovaries had been removed incidentally to pelvic surgery for benign conditions, at least one year prior to the study. None of the women had received estrogen therapy for at least 6 months prior to the study.

After control studies, the patients were given ACTH gel for 3 days. There were definite increases in the urinary estrogen excretion in all cases. Three women were given hydrocortisone for 3 days and none showed any increase in urinary estrogen excretion.

It was concluded that the increase in urinary estrogen excretion in women receiving ACTH is due to direct stimulation of adrenal estrogen excretion rather than a conversion of adrenal steroids to estrogen or an effect of the adrenal steroids on the kidney causing enhanced excretion of estrogen.

J. EDWARD HALL

New England Journal of Medicine

Vol. 259, Sept. 11, 1958.

*Hurst, J. W., Staton, J., and Hubbard, D.: Precordial Murmurs During Pregnancy and Lactation, p. 515.

*Salber, E. J., Stitt, P. G., and Babbott, J. G.: Patterns of Breast Feeding. I. Factors Affecting the Frequency of Breast Feeding in the Newborn Period, p. 707.

Hurst, Staton, and Hubbard: Precordial Murmurs During Pregnancy and Lactation, p. 515.

The authors report 2 specific case histories in which two types of murmur which might be confused with murmurs due to heart disease were noted. The first patient had a precordial systolic murmur first heard during the sixth month of pregnancy, which was thought to be due to a bruit in a branch of the mammary artery, since this artery and its branches enlarge considerably during pregnancy. In the patient described, the unusual finding of persistence of the murmur after delivery was made. Occlusion of a palpable artery in the third left intercostal space near the sternum caused the murmur to disappear instantly. In the second case, a continuous murmur was heard with maximum intensity in the second and third left intercostal spaces near the sternum. When light pressure was applied across the left breast, the murmur disappeared. The authors consider several hypothetical explanations and conclude that this particular murmur was due to a large volume of blood flowing rapidly through the large dilated superficial veins during systole and diastole.

DOUGLAS M. HAYNES

Salber, Stitt, and Babbott: Patterns of Breast Feeding. I. Factors Affecting the Frequency of Breast Feeding in the Newborn Period, p. 707.

The authors investigated the frequency of breast feeding in 114 healthy primiparous women who attended the Family Health Clinic in Boston between 1950 and 1956. The sample was not a random one since it contained an unusual number of college-educated

women. Sixty-two per cent of the women attempted breast feeding. There was no correlation between various factors which were tested for their influence on the mothers' decisions to breast or bottle feed their newborn babies. There was, however, a regional variation in the choice of method of baby feeding, since the mothers born in New England apparently have a greater tendency to bottle feed their babies than mothers born elsewhere in the United States. The authors point out that since most patients have already made up their minds regarding this matter before they come to labor and delivery, if a doctor wishes his patient to try breast feeding the lying-in period is too late for such advice. The most important factors which contributed to a higher percentage of breast feeding were college education of the parents and higher social class. The authors conclude that there is a revival of interest in breast feeding reflected in the greater proportion of women of the middle and upper social classes who breast feed their infants. They attribute this revival to the increasing influence of psychiatric opinion in the United States, even though many doctors still appear to be untouched by psychiatric precepts in this regard.

DOUGLAS M. HAYNES

Obstetrics and Gynecology

Vol. 11, April, 1958.

*Burt, Richard L., and Julian, Nancy: The Utilization of Fructose in Normal Pregnancy and in Preeclampsia, p. 372.

Burt and Julian: Utilization of Fructose in Normal Pregnancy and in Preeclampsia, p. 372.

The reduction of the peripheral utilization of glucose in normal pregnancy has been observed and is known to be pathologically decreased in acute toxemia. It is thought that these changes may be related to a "physiologic insulin resistance . . . which becomes pathologically increased in acute toxemia." This hypothesis is tested by the authors with the use of fructose; for fructose utilization does not depend upon the insulin-sensitive hexokinase, glucokinase but on fructokinase which acts independently of insulin regulation.

Groups of 20 patients, classified as nonpregnant and normally pregnant, as well as 10 patients with acute toxemia, were tested for glucose and fructose levels after standard infusions of each substance. Blood samples were taken every half-hour.

Results indicate that utilization of fructose is hampered to the same degree that glucose intolerance develops in pre-eclampsia. The authors conclude that in spite of the fact that both sugars have different metabolic pathways, the utilization of both is decreased, thus the difference must be more generalized than a local block at the hexokinase level.

L. SONDERS

Vol. 11, June, 1958.

*Snyder, Franklin F.: Pulmonary Hyaline Membrane Contamination of the Lungs by Fluid of the Birth Canal, Studies in Rabbits Demonstrating a Hazard of Obstetric Analgesia, p. 599.

*Watrous, J. B., Jr., Carvalho, M. A., and Ahearn, R. E.: Pitocin Overdosage in the First Stage of Labor—A case report, p. 665.

Snyder: Pulmonary Hyaline Membrane Contamination of the Lungs by Fluid of the Birth Canal, Studies in Rabbits Demonstrating a Hazard of Obstetric Analgesia, p. 599.

Following the administration of various common analgesic agents to pregnant rabbits, the author noted a marked increase in the contamination of the fetal air passages

with the fluid and cells of the birth canal in 95 per cent of 281 autopsies of stillborn rabbits and those that died neonatally. Autopsies performed on a control group of 164 newborn of rabbits that received no analgesia showed no case of massive contamination of the respiratory tree. The agents employed included Demerol, Nisentil, methadone, morphine, and codeine derivatives. A higher incidence of stillbirths and neonatal deaths was observed in the group that received analgesic agents.

The agents were felt to be an important factor in the increased duration of labor and thus prolongation of the exposure of the fetal respiratory tree to the contaminated contents of the birth canal. The entrance of these contents into the air passages was felt to represent evidence of fetal respiration. This debris was said to be the foreign matter in the lungs of newborn. The expansion of the air passages with the entrance of air was shown to cause the displacement of this material along the walls of the alveoli and bronchioles in the form of a membranelike layer. These findings the author offered as a clue to hyaline membrane disease. Atelectasis was often found in the region of the lungs displaying the membranelike layer.

RANDALL D. BLOOMFIELD

Watrous, Carvalho, and Ahearn: Pitocin Overdosage in the First Stage of Labor—A Case Report, p. 665.

The dangers incurred in the use of Pitocin are highlighted in this case report. The authors cite a case in which a tetanic contraction of the uterus ensued subsequently to an inadvertent 1 c.c. intramuscular dose of Pitocin given during the first stage of labor while the patient was under low spinal anesthesia.

The crisis was successfully combated by the use of ether anesthesia with the delivery of a living infant in good condition.

RANDALL D. BLOOMFIELD

Vol. 12, September, 1958.

*Prystowsky, Harry: Fetal Blood Studies: X. A Comparative Study of the Oxygen Capacity of Human Fetal Blood in Normal and Abnormal Pregnancy, p. 264.

Prystowsky: Fetal Blood Studies: X. A Comparative Study of the Oxygen Capacity of Human Fetal Blood in Normal and Abnormal Pregnancy, p. 264.

In the hemochorial placenta of the human the oxygen saturation of intervillous blood is 65 per cent. The fetus lives at a reduced oxygen tension, therefor, and Prystowsky is concerned with the adjustments the fetus makes in normal and abnormal conditions of pregnancy in view of this reduction.

Umbilical vein blood of newborn premature and mature infants at the time of birth was taken, and it was found that there is an increase in the oxygen capacity of cord blood from fetuses 15 to 31 weeks of age, but that from 31 weeks on to 42 weeks there is no significant increase beyond the range of variation and average value. This normal range was not altered in cases of maternal bleeding, early and late, and other conditions known to cause increased anoxia in the fetus.

The concept that the oxygen saturation of umbilical vein blood can be used as an index of fetal hypoxia is negated in view of these findings.

A. STARK WOLKOFF

Proceedings of the Society for Experimental Biology and Medicine

Vol. 98, August–September, 1958.

*Light, A., and Du Vigneaud, V.: On the Nature of Oxytocin and Vasopressin From Human Pituitary, p. 692.

Light and Du Vigneaud: On the Nature of Oxytocin and Vasopressin From Human Pituitary, p. 692.

Oxytocin and vasopressin isolated from posterior pituitary glands of beef and hog are cyclic octapeptide amides. The difference between the vasopressins is one amino acid residue. The beef contains arginine, the hog contains lysine. The oxytocins appear identical but differ from vasopressins in having an isoleucine residue in place of phenylalanine and a leucine residue in place of arginine or lysine.

The pharmacological effects of the above vasopressins differ. The ratio of pressor potency to antidiuretic potency is 1:1 for arginine vasopressin and 6:1 for lysine vasopressin.

A method has been described for the isolation of oxytocin and vasopressin from human posterior pituitary glands. Results of a study indicated that the human oxytocin behaved in a manner identical with that of beef oxytocin after electrophoresis at pH 6.5. The human vasopressin was comparable in chromatographic behavior to beef arginine vasopressin.

The hormones of human posterior pituitary, identified as oxytocin and arginine vasopressin, agree in composition with hormones of beef rather than hog.

DR. P. ROSANELLI

Proceedings of the Staff Meetings of the Mayo Clinic

Vol. 33, Sept. 3, 1958.

*Larson, Norman E., Dockerty, Malcolm B., and Pratt, Joseph H.: Primary Mixed Choriocarcinoma and Dysgerminoma of the Ovary, p. 1.

Larson, Dockerty, and Pratt: Primary Mixed Choriocarcinoma and Dysgerminoma of the Ovary, p. 1.

It is very rare to find elements of both choriocarcinoma and dysgerminoma in the same ovarian tumor. The authors cite 3 cases from the literature and report in detail a case of theirs. In this last case there were abnormal uterine bleeding, positive pregnancy tests, and a pelvic mass, combined with high levels of chorionic gonadotropin.

The tumor of the right ovary was spongy and red. It weighed 300 grams and on cut section was partly cystic and partly solid. There were much hemorrhage and necrosis. Microscopically there were two distinct components, one typical choriocarcinoma and the other fairly typical dysgerminoma.

The signs and symptoms in these cases are due to the tumor mass and the production of chorionic gonadotropin.

Complete surgical extirpation followed by radiation therapy is the treatment of choice. The addition of chemotherapeutic agents may be beneficial.

J. EDWARD HALL

Zentralblatt für Gynäkologie

Vol. 80, July 5, 1958.

*Peters, H.: Comparative Cytologic Examination on Vaginal and Portio Epithelium Relative to Hormone Sensitivity, p. 1049.

Kruschwitz, S.: Rupture of Uterine Varicosity in the Second Half of Pregnancy—A Case Report, p. 1053.

Blumb, W.: The Treatment of Inflammatory Leukorrhea With Gantrisin-Bepanthen Powder, p. 1057.

Knopp, K.: Stenosis of the Fornix and Carcinoma, p. 1061.

Groll, E.: A Hypothesis of Alternating Ovulation, p. 1064.

*Perkedi, J., and Tax, T.: Influencing Rh-Sensitization With Active Immunization by Anti-D Antibodies From Animals, p. 1067.

Tombor, J., and Fodor, T.: Treatment of Starting Premature Labor With Rheopyrin, p. 1068.

Peters: Comparative Cytologic Examinations on Vaginal and Portio Epithelium Relative to Hormone Sensitivity, p. 1049.

Comparative cytologic study of vaginal and ectocervical epithelia in their response to hormones during amenorrhea due to lactation showed that vaginal epithelium is more sensitive to estrogen stimulation. It is, therefore, suggested that smears be taken from both the vagina and the portio in any case where cytologic examination for hormone activity is undertaken during lactation.

WALTER F. TAUBER

Perkedi and Tax: Influencing Rh-Sensitization With Active Immunization By Anti-D Antibodies From Animals, p. 1067.

Rabbits injected with human Rh positive (D) blood produce D-antibodies. Rabbits injected with human Rh-sensitized blood produce anti-anti-D. A precipitation reaction is produced by mixing these sera.

WALTER F. TAUBER

Vol. 80, July 19, 1958.

Lakatos, I.: The Rarer (Uterine) Form of Interstitial Pregnancy—Case Report, p. 1129.

*Wolter, F., and Sternbeck, D.: Results of Therapy of Carcinoma of the Uterus in a Department of Gynecology (of a Non-University General Hospital), p. 1132.

Krimmenau, R.: On the Differential Diagnosis of Increased Atypical Epithelium and Epidermidization of Cervical Polyps—A Case Report, p. 1138.

Hartel, J.: Bilateral Extrauterine Pregnancy (Superfetation). A Case Report, p. 1148.

Wolter and Sternbeck: Results of Therapy of Carcinoma of the Uterus in a Department of Gynecology (of a Non-University General Hospital), p. 1132.

This type of institution differs both from university gynecological departments and from women's hospitals (in Germany). There is no department of radiation therapy and there is only a limited staff. On the other hand, all surgery is done by one or two experienced operators and none by residents.

This series includes 216 carcinomas of the cervix with an uncorrected 5 year cure rate of 51.38 per cent. Corrected for 14 patients lost from follow-up, this figure rises to 55.44 per cent. One hundred seventy-eight patients (82.40 per cent) underwent surgery (Wertheim operation) with a 77.02 per cent 5 year cure rate in Stage I, 49 per cent in Stage II. Only 29.79 per cent of these patients received postoperative x-ray. In 90 cases of carcinoma of the fundus, the 5 year cure rate was 57.07 per cent. Of these patients 84 were treated by surgery with a 61.90 per cent 5 year cure rate.

WALTER F. TAUBER

Correspondence

Comments on X-ray Pelvimetry

To the Editors:

May I be permitted to make some comments on the paper, "X-ray Pelvimetry," by Graber and associates, which appeared in the January, 1959, issue. The authors' views on restricting the indications for pelvimetry (thus sparing mother and fetus unnecessary irradiation), on the limitation of the roentgen method, on the obstetrician's untenable legal position by virtue of a certain type of written report by a certain type of radiologist, on the value of a trial of labor, etc., cannot be questioned, and the authors are to be congratulated on the clarity with which these views were presented.

It is difficult for me to agree that the methods of pelvimetry are "about equal in accuracy." Any method that does not include an axial view of the inlet is not acceptable, for example. This plane of the pelvis is the least susceptible of all to clinical evaluation. Although the transverse and anteroposterior diameters may be normal, aberrations in configuration, such as a severe android tendency, for example, may affect labor.

Aside from the heterogeneity in method, that of the radiologists cannot be disregarded. I have first-hand knowledge that, at least up to 1950, the residents in radiology in one of the world's leading teaching centers in New York had little or no formal training in obstetric roentgenology.

I should like to make a few comments on Table IV:

Point 1: There is no question about the limitations of the x-ray in determining the weight of the fetus. This is an intrinsic shortcoming of the method, to be understood by the obstetrician. The weight of the fetus is determined not only by hard parts (which can be seen) but also by soft parts, which are no more radiologically determinable than the sex of the fetus, except so far as visualizing the fetal subcutaneous fat can give us an idea of the thickness of the fatty layer and of the other soft parts between it and the bone. Limitations such as this should be as well known to the medical fraternity as the inability of the x-ray to determine whether many lesions in the gastrointestinal canal are benign or malignant. Finally, can we be as sure of the clinical evaluation as implied?

Point 2: Those cases of clinically difficult delivery because of inertia certainly should not be included as radiological errors.

Point 3: Any estimation of molding potentiality by the roentgen method is hazardous, as any experienced obstetric roentgenologist will attest. This error, therefore, is not one of method, but one of practitioner.

Point 4: A true error of method, "excusable" if the reader did not say "section indicated, or necessary, etc."

Point 5: A true error of method, and again "excusable" as long as the reader did not say "section must be done, etc."

A few comments on Table V:

1. Error of 50 per cent (1 case) in brow presentation. All will agree this one patient from a total of 2 cannot be treated statistically.

2. Error of 27.7 per cent in previous difficult delivery. This figure means little unless the patients are further subdivided. For example, how many errors involved inertia, something outside the roentgen method?

3. Error of 50 per cent in questionable pelvis. These patients must be further subdivided. (See comments about Table IV.)

4. Error of 55.5 per cent in dystocia. I do not know what the authors encompass by the term. Certainly several of the conditions that they enumerate just above are examples of maternal or fetal dystocia. Any examples of uterine inertia, abnormal maternal soft parts, etc., should not be included since they are properly beyond the roentgen method.

I do not mean to impute to the roentgen method any virtues that it does not have. Just as in its applications in other systems of the body, its limitations must be understood and its findings must be integrated into the fabric of the clinical picture. Consultation between roentgenologist and obstetrician can prove helpful to each other and to the patient. A necessary condition, however, is the interest on the part of the roentgenologist in obstetrics. One interested in following the patients will soon be forced away from the extremes in reporting as he becomes more and more aware of the wonderful compensations of nature. His function will tend to become more and more precautionary rather than visionary. Not putting the obstetrician in a medicolegal hazard by his injudicious reporting should be just part of his good training in radiology.

CHRISTIAN V. CIMMINO, M.D.

MARY WASHINGTON HOSPITAL
FREDERICKSBURG, VA.
JAN. 26, 1959

Reply by Drs. Graber, Barber, and O'Rourke

To the Editors:

We are extremely grateful to Dr. Cimmino for his concurrence with our views on the restriction of the indications for pelvimetry, on the limitations of roentgen pelvimetry, on the untenable legal position of the obstetrician by virtue of certain comments on the x-ray report by some radiologists, on the value of trial labor, etc. We also thank him for his kind comments regarding the clarity of presentation. If we have made our thesis as acceptable to most other radiologists as we have to Dr. Cimmino, we feel that our purpose in writing this paper has been accomplished.

Most medical studies are motivated by some basic force. Ours was undertaken because of the general concept among some obstetricians that the last word as to the management of an obstetrical problem was the x-ray. I am certain that at many monthly conferences of obstetrical departments when cesarean sections are reviewed, the usual question when indications are discussed is, "What did the x-ray pelvimetry show?" or "What was the report of the X-ray Department?"

Clinically, we were not impressed with the correlation between the clinical outcome and the comments of the radiologist regarding the prognosis. We then set out to determine if our clinical impression was correct. The result was the paper submitted.

We would now like to answer the rest of Dr. Cimmino's letter point by point.

Dr. Cimmino does not agree that various pelvimetric methods are "about equal in accuracy." Unfortunately, this statement is taken out of context. What we meant to imply was that we found none of the standard methods used in our community to be especially superior to any of the others. In short, they all had their limitations, although each might be different. Again we repeat what was said originally. "It is concluded that the method used is not as important as the man using it."

Dr. Cimmino brings up the fact that the "heterogeneity of radiologists cannot be disregarded." This is exactly the reason for our wide choice of physicians. Every radiologist to whom these people were referred considered himself competent to take and interpret x-ray pelvimetry. Our correlative results might have been better if all cases had been sent to one special radiologist. This would not be representative because he

would see relatively few cases based on the total deliveries in this area. We wanted a sampling of as much of the radiological community as was practical. The very fact that the results were relatively poor using a wider base merely indicates that perhaps the obstetrical background of some radiologists is limited. If, as Dr. Cimmino says, a great many residents are not being trained in obstetric roentgenology, then we believe that we have done the radiologists and obstetricians a service in bringing this to their attention so that the situation can be corrected.

Answers to comments on Table IV:

1. "There is no question about the limitations of the x-ray in determining the weight of the fetus." Dr. Cimmino also thinks that these limitations should be well known to the medical fraternity. Our only comment is that some radiologists apparently are not aware of this because reports of large baby, small baby, etc., are made rather frequently and, in many cases, these statements are not borne out by the fetal birth weight.

2. Again, words are taken out of context. The statement is "malpresentation, inertia, etc." The comment that precipitated this classification is the statement on the occasional report of "Pelvis adequate for delivery of average size baby." Again, if a cesarean section is done because of deflexed head with an occiput posterior, high in the pelvis, poor labor, slow dilatation, incomplete dilatation, fetal distress, and maternal exhaustion, one might have trouble justifying the section on the basis of the x-ray report. The x-ray said it should come through. The doctor may be accused of doing an unnecessary section. Also, if the baby is larger than anticipated and the pelvis adequate for an average-size baby, but not for the giant infant, inertia frequently occurs. It is probably Nature's way of protecting both mother and baby. Therefore, we believe that inertia may directly be related to cephalopelvic disproportion and definitely deserves to be placed in any discussion of fetopelvic relationships.

3. We agree that any estimation of molding by a radiologist is hazardous and for this reason noted this in our Table. It is our hope that this practice will be discontinued.

4 and 5. We agree that this is a true error of method and that the figures speak for themselves.

Answers to points on Table V:

1. Dr. Cimmino notes that only 2 cases of brow presentation are listed in Table V and this is invalid in so far as numbers are concerned. It was not meant that these be statistically significant. We simply inserted these cases to account for our total figure of 242 cases. Because brow presentation in any series is so low (for which we are grateful!), one would not expect a large number of cases in any series of this size. The doctor is obviously searching for points of argument and takes small insignificant figures and tries to cloud the issue. Our only comment at the end of the table was that x-ray pelvimetry could not measure the fetal head precisely and, therefore, was inadequate and showed the highest percentage of error in the cephalopelvic disproportion group and borderline pelvic group.

2, 3, 4. These comments can be answered together. We again wish to restate our original thesis. Delivery of a baby is a composite mechanism. You cannot disassociate the pelvis from the many other influences that enter into the success of the end result. It should produce an uncompromised mother and child both immediately and at a later date. It is multidisciplined, requiring an evaluation not only of the pelvis, but of the fetal position, attitude, size, normality of structure, axis, etc., plus the mother's parity, age, uterine contractions, soft tissues, emotional stability, hydration, sedation, and fatigue. We, therefore, believe that further subdivision as advocated by Dr. Cimmino would serve no useful purpose. The end results which might be anticipated on the basis of the comments of the reporting radiologist were incorrect in the percentages noted. We simply request that all prognoses and comments relative to the outcome of delivery be eliminated from radiological reports. Because so many other factors enter into the final outcome we believe that the radiologist is ill advised in stating an opinion.

The last paragraph of Dr. Cimmino's letter expresses our views adequately. We agree with and would like to re-emphasize some of his points. A pelvic x-ray should be

ideally examined by both a radiologist and obstetrician. This is not always practical because babies come at unfortunately inconvenient hours.

When an x-ray report is placed on a patient's chart, it should not in any way compromise the judgment of the obstetrician or intimidate him in any fashion. Similarly it should not place him in any untenable or precarious position medicolegally. If this paper has created an atmosphere that will make the function of the average radiologist more precautionary than visionary, we feel that it was worth while.

We thank Dr. Cimmino for his interest, and we thank him for upholding our position and allowing us to restate our position.

EDWARD A. GRABER, M.D.
HUGH R. K. BARBER, M.D.
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Obstetrical Forceps Using New Principle of Parallelism

To the Editors:

In the February, 1959, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, I read with greatest interest the article of Dr. Wallace B. Shute about the obstetrical forceps with the use of the *new* principle of parallelism. The idea of parallel blades instead of crossed blades is excellent and has many advantages, as outlined by E. Ekstein,[1] who reported in 1923 enthusiastically about an obstetrical forceps with parallel blades which had been invented and described by N. J. A. F. Boerma,[2] a gynecologist in Groningen, in 1907. The blades of Boerma's forceps run *parallel to each other* and are united at the end by a simple lock. Personally, I have used this handy instrument in many cases with excellent results and great satisfaction.

I am sure the knowledge of Boerma's paper, which Shute missed in his brief survey of the historical development of the major principles in the obstetrical forceps from Hippocrates to the present, will offer him many suggestions for valuable modifications.

With respect to the footnote on page 443, I feel strongly that credit must be given to Boerma and Ekstein for their creative pioneer work.

References

1. Ekstein, E.: Zentralbl. Gynäk. **47**: 85, 1923.
2. Boerma, N. J. A. F.: Zentralbl. Gynäk. **31**: 565, 1907.

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Reply by Dr. Shute

To the Editors:

I read Dr. Tauber's letter with great interest and am indebted to him for bringing to my attention the reports of Boerma and Ekstein on an instrument of which I was previously unaware. I agree with the writer that Boerma deserves historical mention since he demonstrated an acute perception of the grave dangers to fetal heads from use of the scissors lock in forceps. As the photographs of his instrument show in his original paper, he attempted an improvement in this principle by greatly lengthening the shanks and articulating them by a hinge lock at their proximal ends. From the fulcrum of this mechanism, the blades move in an arc in and outward to match the size of each head and are held in apposition to it only by the grasp of the operator's hand upon the shanks (Fig. 1). By this evasion, however, Boerma did not escape the basic error of the scissors' mechanism in producing inaccurate fitting and improper pressures. He merely reduced and transferred the pressure usually exerted upon the handles below a scissors lock to the

elongated shanks above his hinge lock. Moreover, with blades diverging freely from the fulcrum of a hinge, however long the shanks, parallel application of blades to heads of varying sizes is mechanically impossible to achieve. Exact parallelism between the blades of a forceps at any distance apart can be achieved only by linear translation of their movement at right angles to the axis of the blades as exists in the parallel forceps described in my paper of February, 1959. All other locking mechanisms including Boerma's produce an angular translation of movement of the blades from a single fulcrum as shown in the diagram. It is therefore apparent from even the most cursory glance that Boerma's instrument was neither designed as a parallel forceps nor capable of being used as such. In fact in their papers neither Boerma nor Ekstein ever made any such claim. I am sure it would be of further interest to Dr. Tauber to know that patent applications for the parallel forceps have been allowed in Germany (where Boerma's article was published and where his forceps is in use) and in Great Britain.

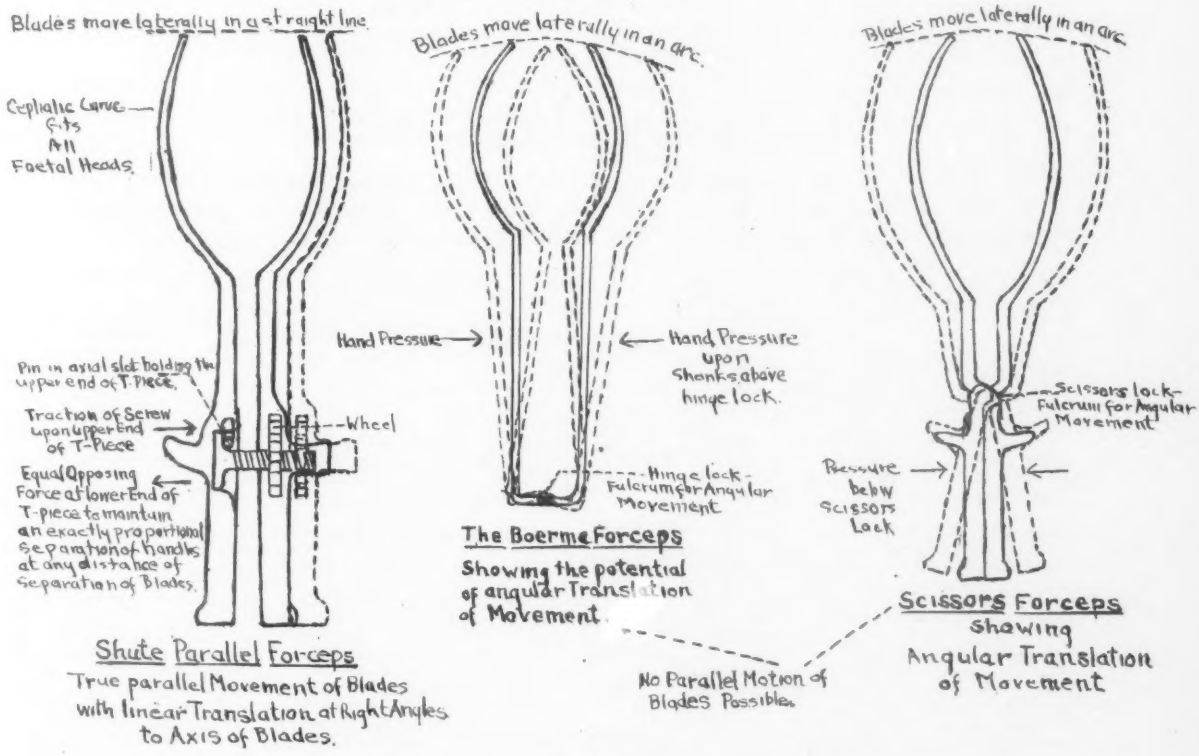
Blades move laterally in a straight line
Cephalic Curve — Fits All Foetal Heads
Pin in axial slot holding the upper end of T-piece
Traction of Screw upon Upper End of T-Piece
Wheel
Equal Opposing Force at lower End of T-piece to maintain an exactly proportional separation of handles at any distance of separation of Blades.
Shute Parallel Forceps
True parallel Movement of Blades with linear Translation at Right Angles to Axis of Blades.
Blades move laterally in an arc.
Hand Pressure
Hand Pressure upon Shanks above hinge lock.
Hinge lock - Fulcrum for Angular Movement
The Boerma Forceps
Showing the potential of angular Translation of Movement
Blades move laterally in an arc.
Scissors lock - Fulcrum for Angular Movement
Pressure below Scissors Lock
Scissors Forceps
Showing Angular Translation of Movement
No Parallel Motion of Blades Possible.

Diagram comparing the Parallel Movement of The Shute Forceps With the Angular Movement of the Boerma and Scissors Forceps

Fig. 1.

For those who, like Dr. Tauber, are interested in this practical application of the parallel principle, a 30 minute color film has been prepared to demonstrate the clinical advantages of the parallel forceps in all types of instrumental delivery. This film can be obtained on request for group showings from the Professional Services Department of Weber Pharmaceuticals, Limited, 393 Weston Drive, Toronto, Canada.

May I again express my gratitude to Dr. Tauber for his kindness in furnishing this additional evidence of our priority in the use of the principle of parallelism in obstetrical forceps.

WALLACE B. SHUTE, F.R.C.S.(C)

276 ELGIN STREET
OTTAWA, CANADA
MARCH 6, 1959

Item

Society for the Scientific Study of Sex

The Society for the Scientific Study of Sex will hold its second annual meeting on Nov. 7, 1959, at the Barbizon Plaza Hotel, New York City. There will be two symposia on the topics "What Is Sexually Normal?" and "Psychological Factors in Infertility."

Robert V. Sherwin, Executive Secretary
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Erratum

In the discussion by Dr. W. R. C. Tupper of the paper, "Management of Recurrent Carcinoma of the Cervix," by E. J. Love and H. H. Allen, in the March, 1959, issue of the Journal, page 544, in the line above the table, the phrase "Wertheim hysterectomies with no node dissections" should read "Wertheim hysterectomies with node dissections."

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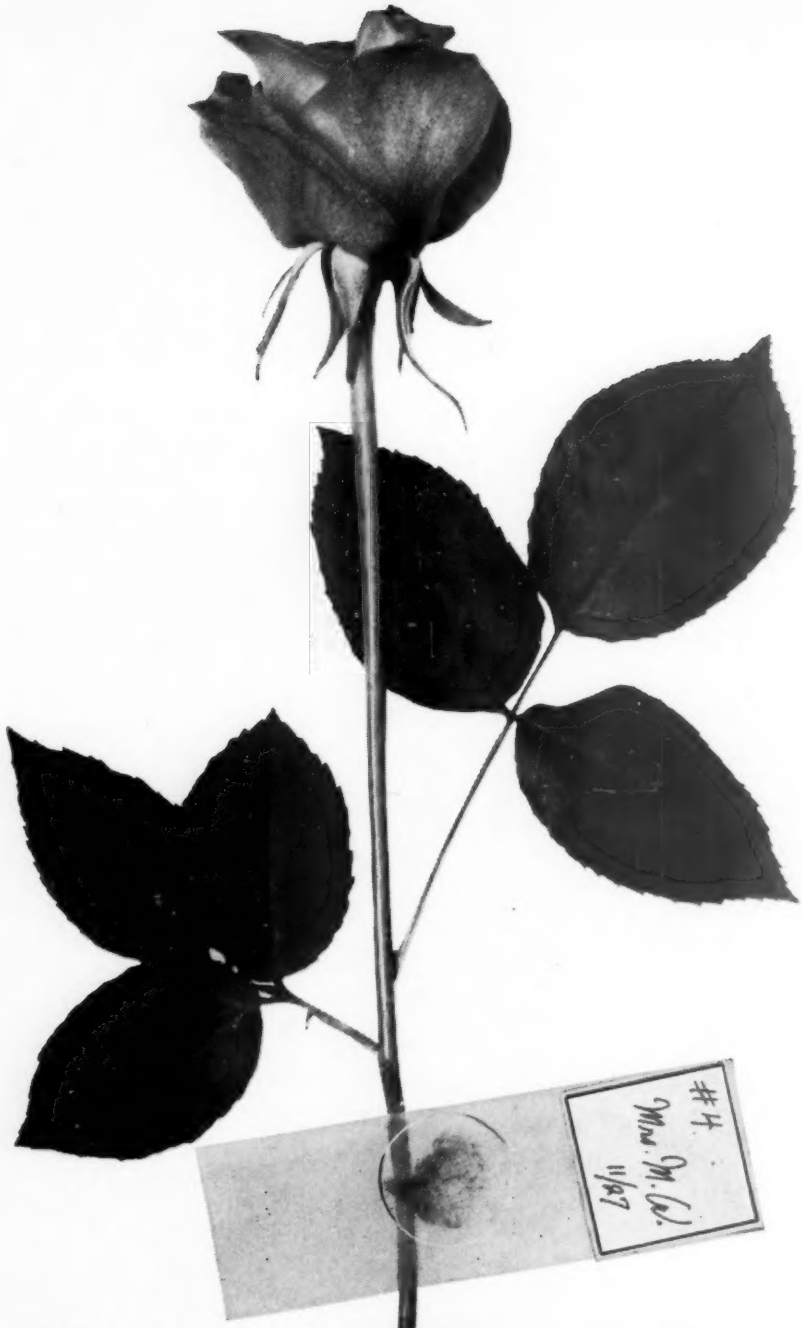

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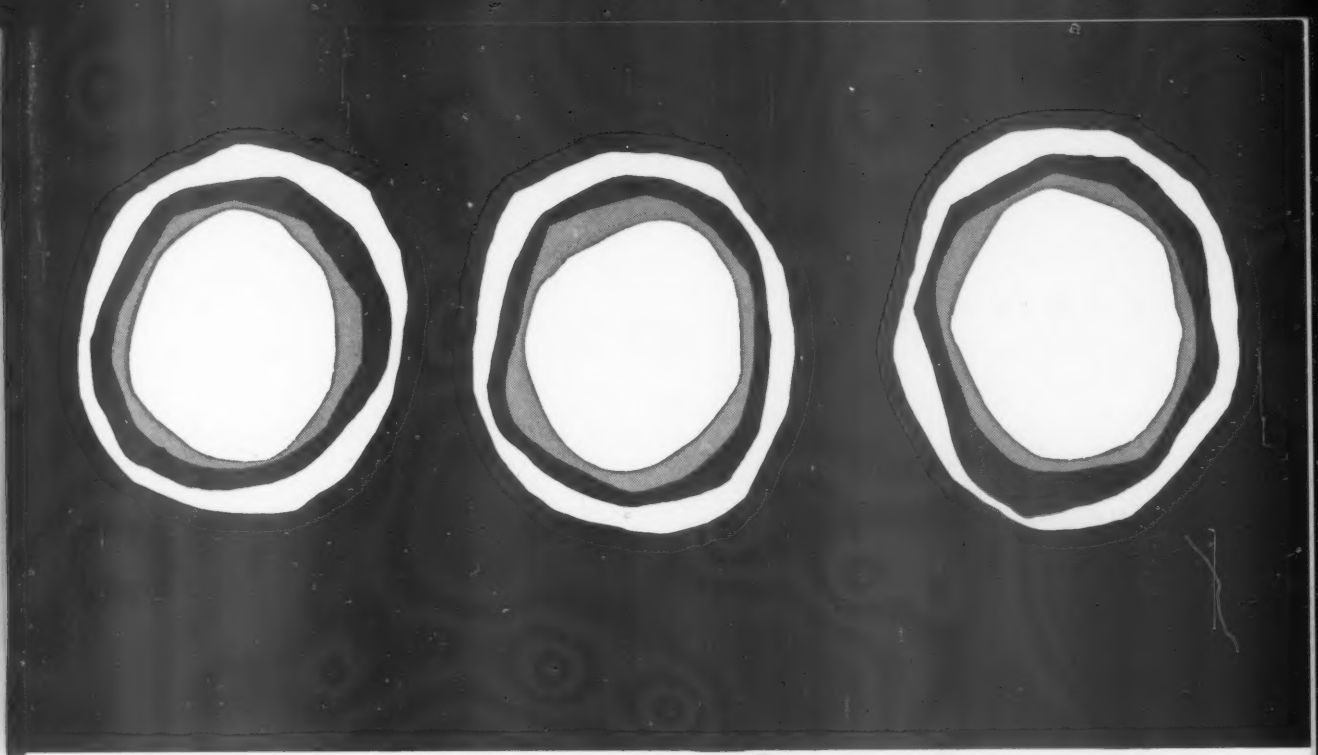

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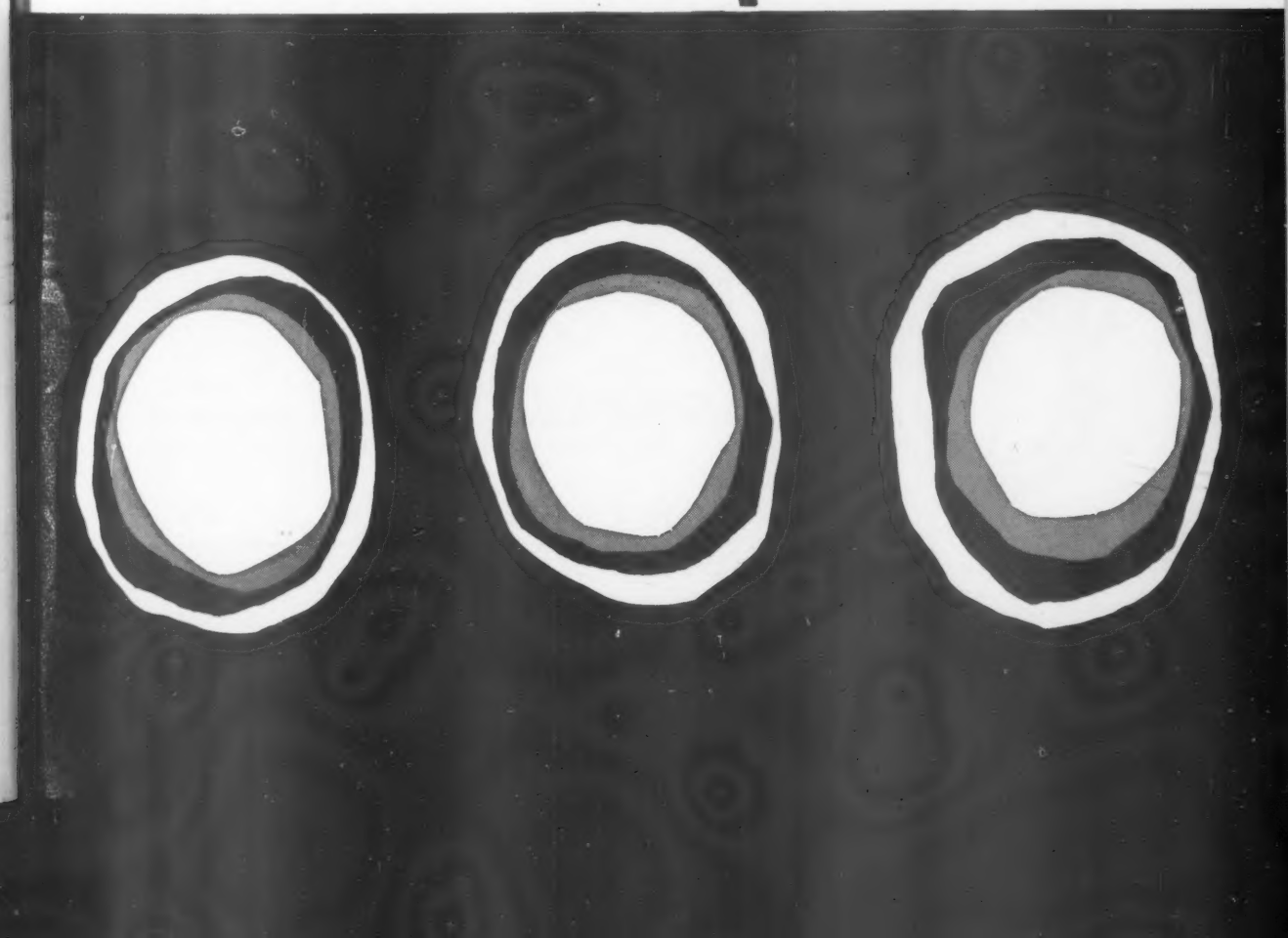

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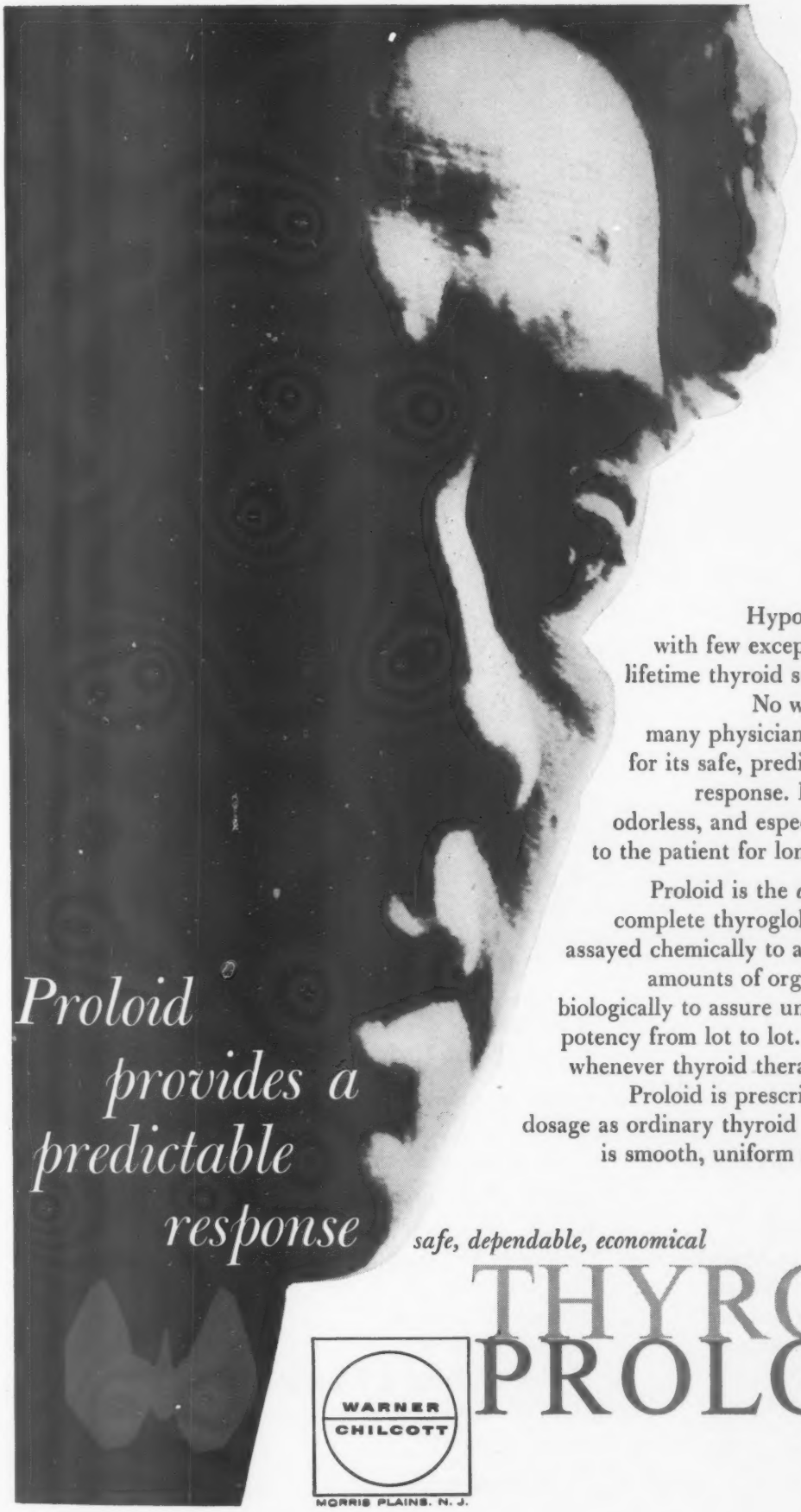

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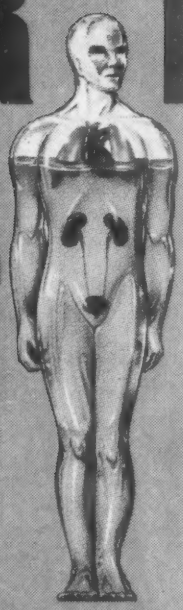

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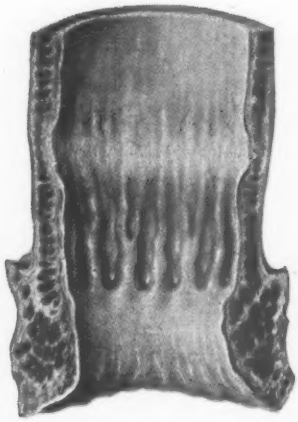

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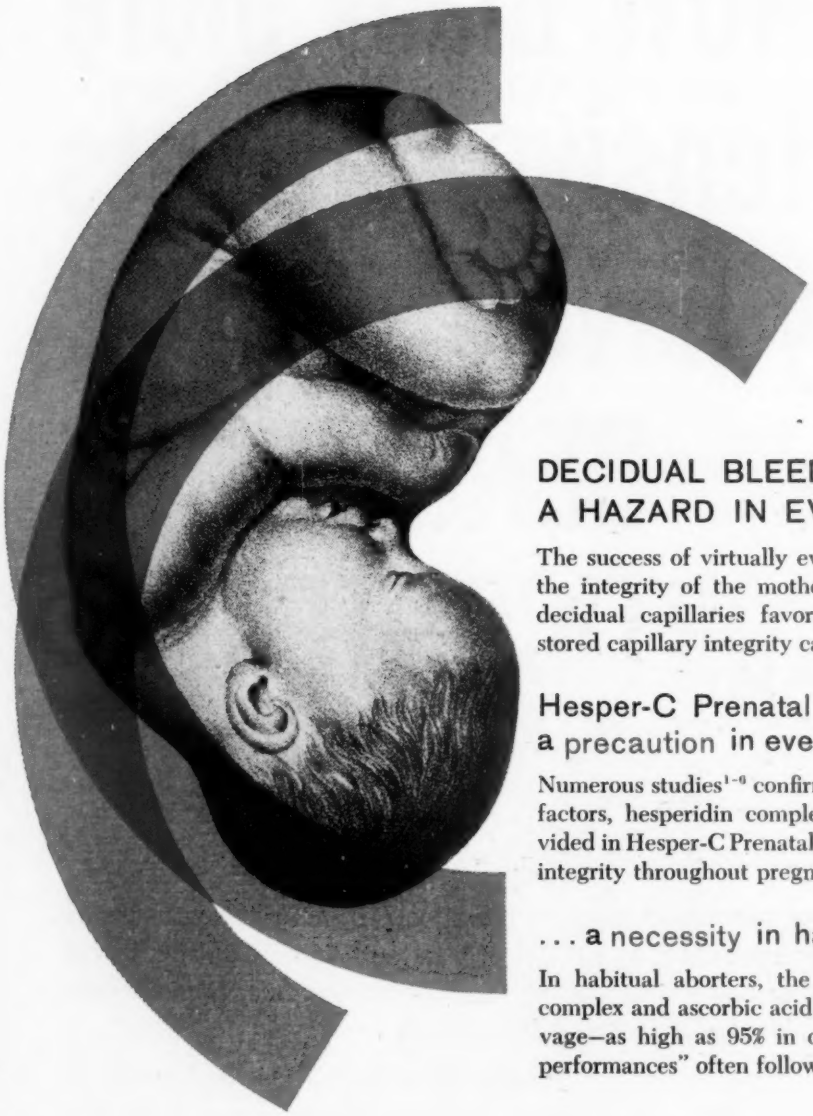

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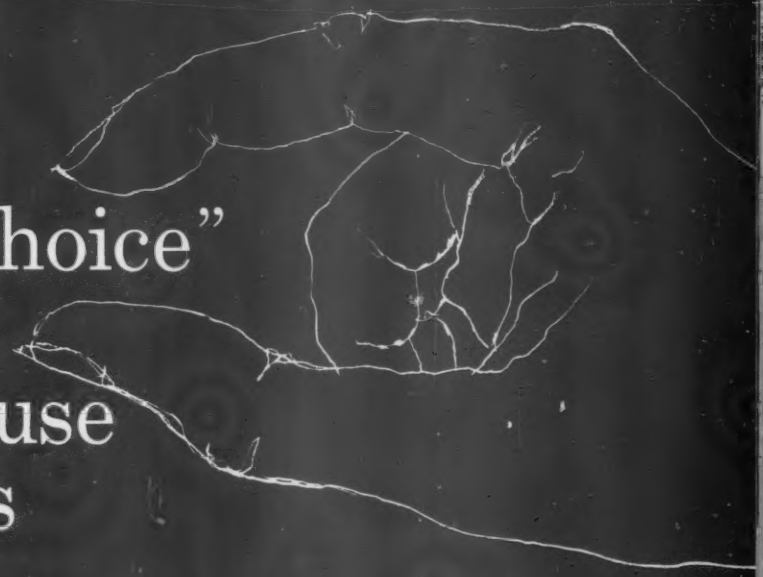

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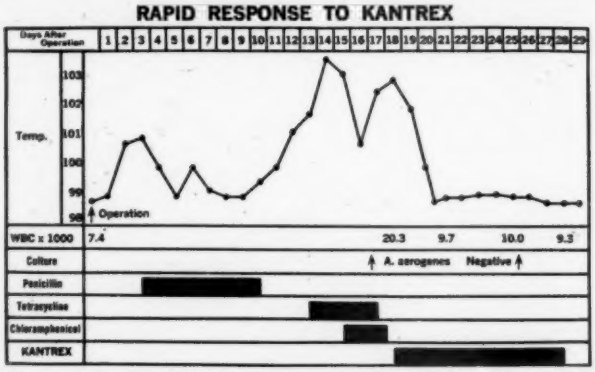

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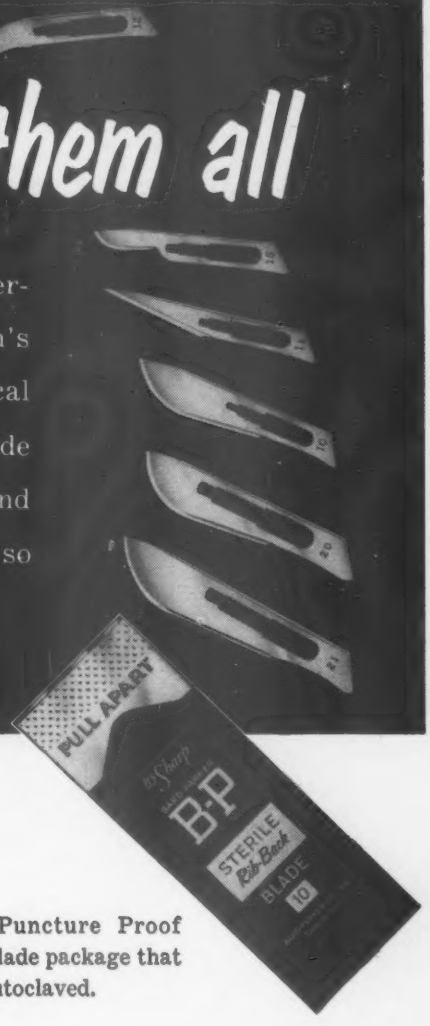

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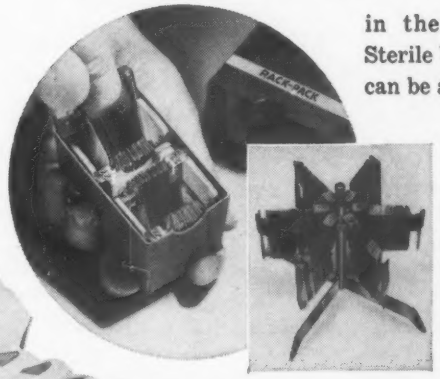

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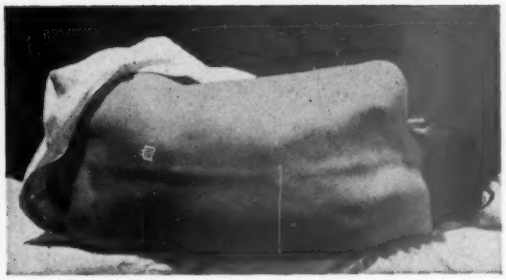
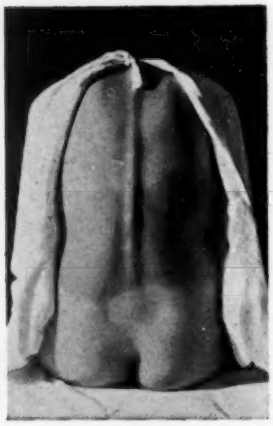




"SADDLE BLOCK" ANESTHESIA

XYLOCAINE HAS THESE ADVANTAGES –

- Low binding affinity minimizes potential nerve injury.
- Anesthetic effect is routinely rapid, profound and well tolerated.
- It is completely stable in the presence of spinal fluid.

The duration of "Xylocaine spinal" (60-90 minutes, followed by an additional 40 minutes of analgesia) is ideally suitable for obstetrical, gynecological and urological procedures, and for surgery of the lower abdomen. Complete information regarding administration and dosage available on request.

Specially packed for spinal anesthesia in 2 cc. color break ampules; Xylocaine HCl 5% with glucose 7.5%, a sterile hyperbaric solution sp.g. 1.030-1.035.

ASTRA PHARMACEUTICAL PRODUCTS, INC., WORCESTER 6, MASS., U.S.A.

XYLOCAINE® HCl 5%

(brand of lidocaine*)

WITH GLUCOSE 7.5%

SEE PDR

*U.S. PAT. NO. 2,441,498 MADE IN U.S.A.

to meet her greater needs for diet supplementation

Natalins® Comprehensive

Vitamins and minerals, Mead Johnson

Natalins® Basic

Vitamins and minerals, Mead Johnson

both extra generous in iron, ascorbic acid and calcium

In a study[1] of over a thousand obstetrical patients, anemia was found to occur with 50% greater frequency in multiparas than in primigravidas. And it was found that anemia often indicates other nutritional deficiencies as well . . . Natalins Comprehensive tablets supply 12 vitamins and minerals and Natalins Basic tablets supply 4 vitamins and minerals . . . both are formulated to meet the special needs of multiparas by supplying generous amounts of elemental iron (40 mg. per tablet), ascorbic acid (100 mg. per tablet) and calcium (250 mg. per tablet).

Convenient, one-a-day tablet dosage.

Mead Johnson
Symbol of service in medicine

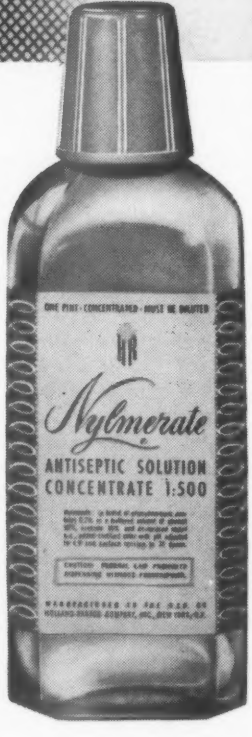
1. Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61: 71-74 (Jan.) 1951

NA-1059M

Nylmerate Solution Concentrate as a vaginal douche helps prevent recurrences of vaginal discharges, acts as an effective prophylaxis.

- Available only on your prescription (eliminates possibility of excessive or unwarranted vaginal douching)
- Therapeutic (Bactericidal and trichomonacidal)
- Acidic (4.1 pH in dilution)
- Reaches innermost recesses via low surface tension
- Soothing
- Use . . . twice daily (1 capfull to 2 quarts water) prior to insertion of medication
- Economical

Specify pint bottles with measuring cap (Nylmerate: A brand of phenylmercuric acetate)



As a concomitant measure—

NYLMERATE IMPROVED JELLY

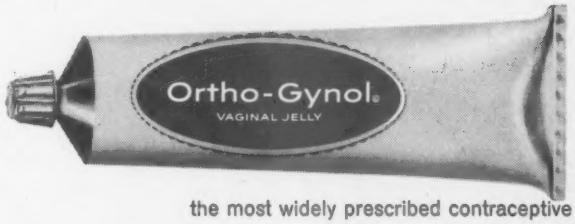
- Positive Trichomonacidal and Monilicidal action
- Symbiotic organisms eradicated by its bactericidal potency
- Low surface tension allows for deep epithelial cell penetration
- Re-establishes normal vaginal flora and prevents recurrences
- Simple to use . . . morning and night applications, including treatment during menstrual period

Prescribe: "Nylmerate Jelly with applicator" 3 oz. and 5 oz. tubes

HOLLAND-RANTOS CO., INC. • 145 HUDSON STREET • NEW YORK 13, N. Y.

while she is planning
her family,

she needs your help
more than ever



the most widely prescribed contraceptive

Ortho

WHENEVER A DIAPHRAGM IS INDICATED

specially designed for closure of the incompetent cervix

new MERSILENE* LIGATURE

- Retains its strength . . . is not absorbed.
- Double thickness of MERSILENE with heat-sealed edges for added strength and ease of use.
- Maintains its flatness and does not cut through wall of cervix.
- Is easily prepared — just autoclave.

MERSILENE Ligature for the Incompetent Cervix. Double thickness Mersilene ligature, 5 mm. wide and 30 cm. long, packaged in convenient plastic box. Code No. R-5 mm.

*Mersilene is the ETHICON Trademark for polyester fiber.

ETHICON®

In hypoprothrombinemia

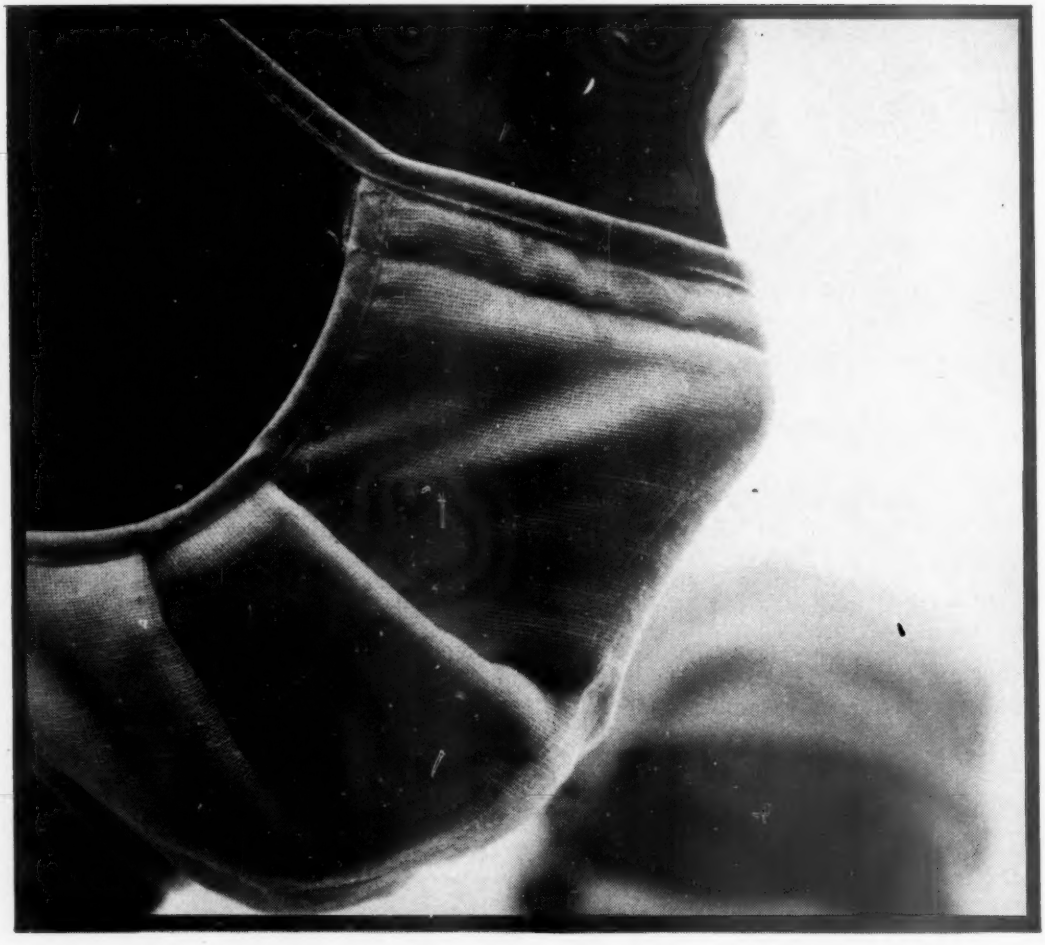
KONAKION

Rapid action	rate of absorption faster than menadione or derivatives... more potent and lasting effects.
Wide margin of safety	substantially safer than vitamin-K analogues—no kernicterus reported.
Versatility of administration	capsules for oral use...fine aqueous dispersion for parenteral administration.
Compatibility	unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.
Low dosage forms	no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®—brand of vitamin K_1 ROCHE® Capsules—5 mg; Ampuls—1 mg/0.5 cc

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey



in surgical and obstetrical procedures
where apprehension increases tension...
patients respond well to

VISTARIL®

hydroxyzine pamoate

EFFECTIVENESS AND SAFETY Vistaril establishes relaxed indifference to preoperative preparation without serious hypotensive effects.

PSYCHOTHERAPEUTIC POTENCY Vistaril makes possible the maintenance of an adequate degree of narcosis with reduced doses of narcotics.
Vistaril relieves tension and controls emesis in both postoperative and postpartum patients.

Recommended Oral Dosage: up to 400 mg. daily in divided doses.

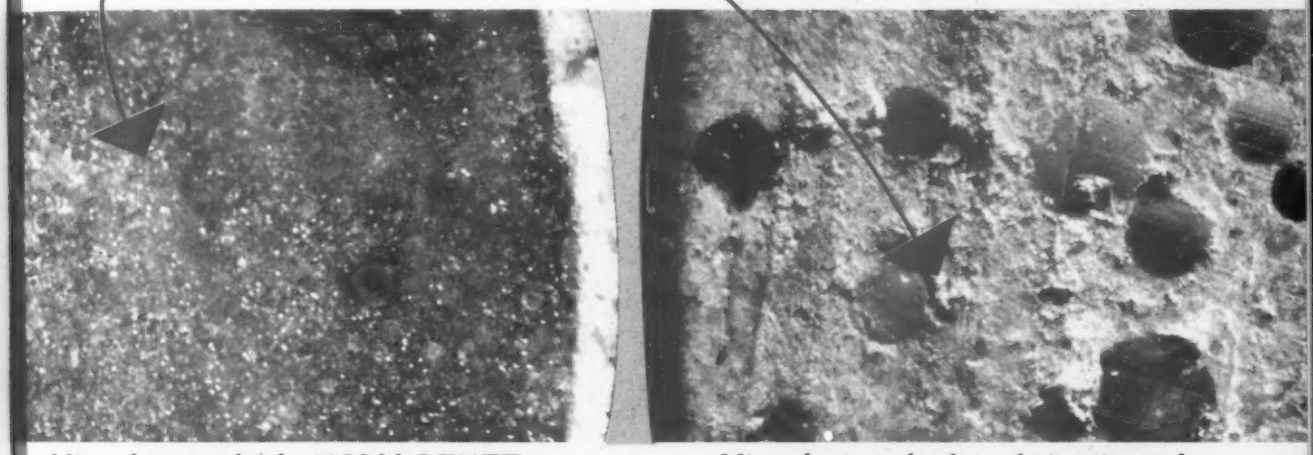
Recommended Parenteral Dosage: 25-50 mg. (1-2 cc.) I.M., q. 4 h., p.r.n.

Vistaril is supplied in 25 mg., 50 mg., and 100 mg. capsules. The parenteral solution is available in 10-cc. vials and 2-cc. Steraject® cartridges; each cc. contains 25 mg. hydroxyzine (as the HCl).

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York

HOMOGENIZATION makes the difference



Microphotograph of a **HOMAGENET**

Microphotograph of usual vitamin product

The photographs above point out the difference between Homagenets and many vitamin products. By means of the homogenization process, both oil and water soluble vitamins are presented in microscopic particles. Due to the fine particle size, there is much greater surface exposure, which permits quicker absorption and better utilization. This has been clinically proved by Lewis and others.[1]

1. Lewis, J.M., et al.: J. Pediatrics, *31*:496

HOMAGENETS®

The only homogenized vitamins in solid form

THE S.E. MASSENGILL COMPANY Bristol, Tennessee

Here
are the advantages
of

HOMAGENETS®*

the only
homogenized vitamins
in solid form

The advantages of HOMAGENETS

- Pleasant, candy-like flavor
- Better absorbed, better utilized
- Excess vitamin dosage unnecessary
- Longer storage in the body
- No "fishy burp"
- May be chewed, swallowed or dissolved in the mouth.

HOMAGENETS are available in five formulas:

PEDIATRIC—Children like the orange-flavored, candy-like taste.

PRENATAL—Contains iron and calcium as a dietary supplement during gestation.

GERIATRIC—A complete formula for the prevention of vitamin-mineral deficiencies.

AORAL—Useful in the treatment of certain types of skin disorders.

THERAPEUTIC—Particularly indicated during convalescence and stress periods.

*U.S. Pat. 2676136. Other Pat. Pending

Currently, mailings will be forwarded only at your request. Write for samples and literature.

THE S.E. MASSENGILL COMPANY Bristol, Tennessee · New York · Kansas City · San Francisco

peridural anesthesia without "spottiness"

THE MORE YOU EXPECT OF A LOCAL ANESTHETIC THE MORE YOU WILL DEPEND ON XYLOCAINE
Peridural Block 523
Peridural anesthesia with Xylocaine is free from "spottiness" because of the high diffusibility and profoundness which are characteristic of this agent. These properties, together with rapid onset and excellent tolerance, make Xylocaine your preferential agent in all peridural techniques.
Available: 30 cc. vials, single dose... 0.8% and 1.2% without epinephrine and with epinephrine 1:200,000

Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U S. A.

ASTRA

XYLOCAINE® HCl

(brand of lidocaine®)

Sterile solution for injection

SEE PDR

®U S. Pat No 2,441,498 Made in U S A

Uneventful Recovery

the pattern of

GLUCOSAMINE-POTENTIATED TETRACYCLINE

therapy

COSA-TETRACYN*

capsules
125 mg., 250 mg.

oral suspension
orange flavored, 2 oz. bottle, 125 mg. per teaspoonful (5 cc.)

pediatric drops
orange flavored, 10 cc. bottle (with calibrated dropper), 5 mg. per drop (100 mg. per cc.)

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

*Trademark for glucosamine-potentiated tetracycline

NOTE:
Rapid and high initial antibiotic blood levels are an important factor in uneventful recoveries. Glucosamine potentiation provides the fastest, highest tetracycline levels available with oral therapy. Bibliography and professional information booklet available on request.

Just one prescription for Engran "Term-Pak" (270 TABLETS)

SQUIBB VITAMIN-MINERAL SUPPLEMENT

calling for one tablet a day will carry her through term to the six-week postpartum checkup. This means you are assured of a nutritionally perfect pregnancy, and she realizes major savings.*

SQUIBB *Squibb Quality — the Priceless Ingredient*

'ENGRAN'® 'TERM-PAK' AND 'FLEXIDOSE' ARE SQUIBB TRADEMARKS

* *And when baby comes, specify* Engran baby drops — *full* vitamin support in *half the volume* of most similar preparations — lasts twice as long. Supplied in 15 cc. and 50 cc. bottles. Convenient 'Flexidose' Dropper assures accurate dosage.

Overeating was Mrs. Hyde's substitute for the family life she used to have. The morning coffee klatsch carried her 'til the afternoon bridge game, when she nibbled on snacks until dinner. Now an Ambar #1 Extentab each morning controls her nibbling, while the temptations of social eating are overcome with a timely supplementary **Ambar Tablet,** 3.33 mg. methamphetamine hydrochloride and ⅓ gr. phenobarbital.

Overweight Mrs. Geller rebelled at the monotony of housekeeping chores and the antics of her school-age children added tension to boredom. Eating became an outlet for her emotions. A daily **Ambar #1 Extentab,®** an artful balance of 10 mg. methamphetamine hydrochloride and 1 gr. phenobarbital, not only curbed her appetite, but by aiding in a renewal of creative interests, tempered her reactions to minor irritations.

Obesity and Mrs. Adams seem inseparable. She has tried all the current diet fads her friends, relatives, and the newspapers tell her to try, and she says they don't work. She knows how unrelenting are the frustrations that drive her to overeating. She can use the more potent dose of the 15 mg. methamphetamine hydrochloride with 1 gr. phenobarbital in **Ambar #2 Extentabs.®**

Successful Mr. Holt runs a fine business and eats lunches and dinners in the best restaurants. He attacks his food with the same determination that made him a business success. Because eating is his outlet for the minor anxieties and frustrations of an active life, he has eaten his way into a health problem. An **Ambar** regimen will help control his appetite and at the same time lift his mood.

AMBAR™ (methamphetamine and phenobarbital) A.H.Robins Co.,Inc.Richmond 20,Virginia

Robins

In Kraurosis and Leukoplakia Vulvae,
Pruritis Vulvae et Ani, Postmenopausal
and Senile Vaginitis . . .

HIST-A-CORT-E®

CREME pH 4.7

ACID MANTLE® · HYDROCORTISONE · ESTRONE · PYRILAMINE MALEATE · SYNTHETIC VITAMIN A

DOME

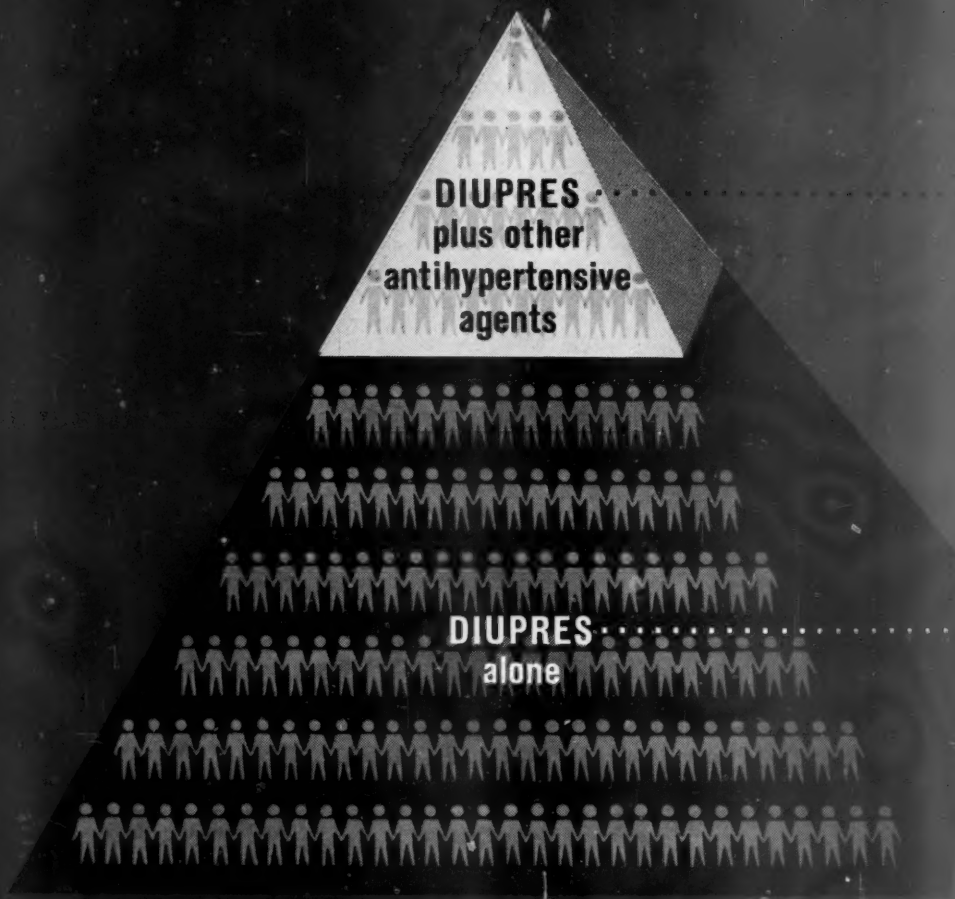
Stops itching instantly and completely.
Corrects thickening of skin—eliminates scaling.
Restores skin to normal softness and pliability.
Tends to negate necessity for surgery
in Kraurosis and Leukoplakia Vulvae.

Supply: With ½% hydrocortisone in ½ oz. and 1 oz. tubes
With 1% hydrocortisone in ½ oz. tubes
Sig: Apply twice daily *Samples and literature on request*

INCORPORATED IN EXCLUSIVE ACID MANTLE VEHICLE

THE MOST TRUSTED NAME IN DERMATOLOGICALS

DOME CHEMICALS INC.
125 West End Avenue, New York 23
665 N. Robertson Blvd., Los Angeles 46 · 2765 Bates Road, Montreal



with DIUPRES
fewer patients
require additio
of other anti-
hypertensive
agents

DIUPRES
is adequate
by itself
for many
hypertensives

DIUPRES PROVIDES "BROAD-BASE" ANTIHYPERTENSIVE THERAPY
... is effective by itself in a majority of patients with mild or moderate hypertension, and even in many with severe hypertension

greatly improved and simplified management of hypertension

DIUPRES*

DIURIL® WITH RESERPINE

the first "wide-range" antihypertensive—effective in mild, moderate, and severe hypertension

- more hypertensives can be better controlled with DIUPRES alone than with any other agent . . . with greater simplicity and convenience, and with decreased side effects
- can be used as total therapy or primary therapy, adding other drugs if necessary
- in patients now treated with other drugs, can be used as replacement or adjunctive therapy
- should other drugs need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced
- organic changes of hypertension may be arrested and reversed . . . even anginal pain may be eliminated
- patient takes one tablet rather than two . . . dosage schedule is easy to follow
- economical

DIUPRES-500 500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. One tablet one to three times a day.

DIUPRES-250 250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. One tablet one to four times a day.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

*DIUPRES AND DIURIL (CHLOROTHIAZIDE) ARE TRADEMARKS OF MERCK & CO., INC.

Proved hematinic efficiency

"... buffered ferrous sulfate in uncoated tablets is the best all-around medicament for use in iron deficiency states."[1]

Fermalox

tablets (RORER)

BUFFERED FERROUS SULFATE

high absorption

low dosage

well tolerated

"Buffered ferrous sulfate in uncoated tablets (Fermalox) has a high absorption index, as determined by use of radioactive iron (Fe^{59}) as a tracer. Reticulocyte and hemoglobin response to buffered ferrous sulfate is highly satisfactory. When this preparation is prescribed, clinical response is obtained with 44% of the dosage of ferrous sulfate recommended by the Pharmacopeia of the United States. The adverse reactions of nausea, burning sensations, diarrhea, and abdominal cramps are almost completely avoided by use of buffered ferrous sulfate."[1]

Each FERMALOX tablet contains: Iron sulfate, principally ferrous 0.2 Gm.; MAALOX® (magnesium and aluminum hydroxides) 0.2 Gm.

Dosage: 2 tablets daily for satisfactory hematopoiesis.

Offered: bottles of 100 at prescription pharmacies.

1. Price, A.H., *et al.:* J.A.M.A. *167*:1612, 1958.

Hematinic efficiency *plus* tonic stimulation

Fermatin

capsules (RORER)

TONIC IN A CAPSULE

FERMATIN capsules taken twice daily provide *the tonic stimulation of essential hematopoietic factors*, potentiated with D-SORBITOL and MAALOX.®

Each FERMATIN capsule contains: Ferrous Sulfate 0.2 Gm.; MAALOX®—RORER (magnesium and aluminum hydroxides) 0.2 Gm.; Folic Acid 1.5 mg.; Ascorbic Acid 75 mg.; Cobalamin Concentrate N. F. (Vitamin B_{12} Activity 7½ mcg.) 7.5 mg.; D-SORBITOL (absorption enhancement factor) 0.15 Gm.

Offered: bottles of 100 and 500 capsules, at prescription pharmacies.

RORER

WILLIAM H. RORER, INC. PHILADELPHIA 44, PA.

the true specific
for
monilial vaginitis

GENTIA®-JEL

CURES ARE QUICKER Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. *IMMEDIATE RELIEF* This soothing jel provides fast, gratifying relief of vulvar itching and burning . . . destroys fungi and bacteria. *COMPLETE COVERAGE* Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.

start therapy
with GENTIA-JEL
. . . it works
when others fail

WESTWOOD PHARMACEUTICALS Buffalo 13, New York

GENTIA®-JEL

the true specific for monilial vaginitis

Gentian violet is the most effective agent known for the destruction of Monilia albicans. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monilial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never reused, but discarded.

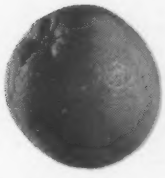
And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

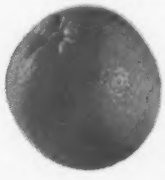
Gentia-jel is supplied in packages of 12 single dose disposable applicators.

WHY WAIT UNTIL OTHER THERAPIES FAIL . . .
START YOUR PATIENTS WITH GENTIA-JEL

WESTWOOD PHARMACEUTICALS Buffalo 13, New York



lifesaving technique for the unborn



includes high citrus intake

Abortion-prone mothers deliver live babies in nearly 9 out of 10 pregnancies

Reporting on 134 pregnancies in 100 habitual abortion patients, Javert* describes a management program that resulted in live deliveries in all but 16 pregnancies. The previous 95.2 per cent rate of spontaneous abortions was reduced to 11.9 per cent by his comprehensive regimen which includes a high citrus intake (supplying up to 350 mg. of vitamin C daily), supplemented by 150 mg. of ascorbic acid and 5 mg. of vitamin K daily. Javert believes these antihemorrhagic vitamins "serve as a 'never-leak' . . . keeping physiologic decidual hemorrhage from becoming pathologic."

AVERAGE CITRUS INTAKE TO SUPPLY 350 MG. VITAMIN C

	or	*or*
28 oz. orange or grapefruit juice	1 grapefruit 2 oranges 2 tangerines	½ grapefruit 1 orange 16 oz. orange juice

Florida Citrus Commission Lakeland, Florida

Florida Citrus
ORANGES • GRAPEFRUIT • TANGERINES

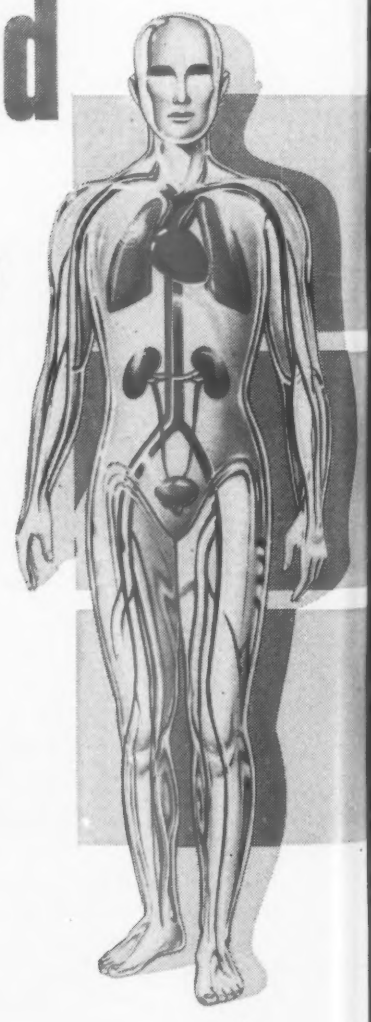
*Javert, C. T.: Obst. & Gynec. 3:420, 1954; Cf. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

NEW

HYDRO DIURIL™

(HYDROCHLOROTHIAZIDE)

simplifies* and improves any regimen for hypertension



*it's as easy as 1, 2, 3 to use

HYDRODIURIL™

(HYDROCHLOROTHIAZIDE)

1 Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

2 Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.
Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.

MSD MERCK SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.

for pre- and post-partum management of constipation

TARGET ACTION specifically on the large bowel

DORBANE

(1,8-dihydroxyanthraquinone)

selective peristaltic stimulant

▪ smooth, overnight action ▪ no griping ▪ well tolerated, non-habituating

Available in 75 mg. scored tablets and suspension.

WHERE STOOL SOFTENING IS ALSO INDICATED

DORBANTYL® FORTE

(Dorbane, 50 mg.* + dioctyl sodium sulfosuccinate, 100 mg.)*

Double-strength capsules for maximum economy and convenience.

DORBANTYL®

(Dorbane, 25 mg.* + dioctyl sodium sulfosuccinate, 50 mg.)*

For lower dosage and in children.

Available in capsules and suspension.

***In proportions proved optimal by clinical trial in over 550 cases.**

(Marks, M. M.: Clin. Med. 4:151, 1957.)

SchenLabs

SCHENLABS PHARMACEUTICALS, INC., NEW YORK 1, N.Y.

Manufacturers of NEUTRAPEN® for penicillin reactions.

®TRADEMARKS REG. U. S. PAT. OFF. DORBANTYL FORMULA PATENTED. 55559

the instant cooling relief of

METI-DERM Aerosol

"Meti" steroid topical

and when infection is a factor

METI-DERM with Neomycin Aerosol

especially for

HARD-TO-TREAT PATIENTS

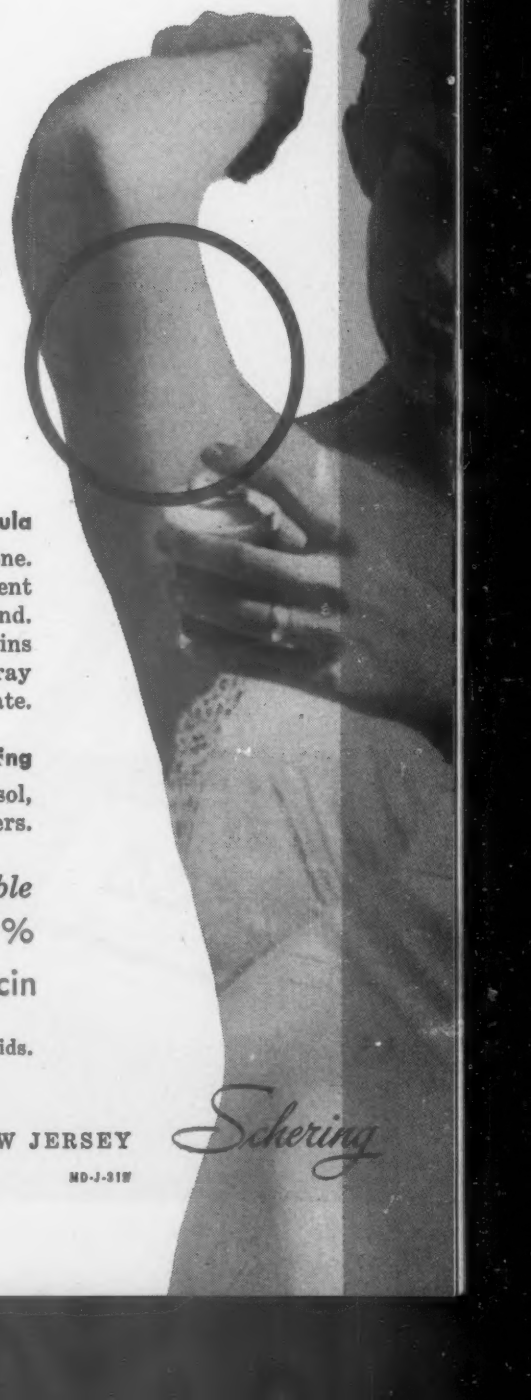
e.g.: jumpy, refractory children..."spray magic" fascinates them.

HARD-TO-TREAT DERMATOSES

e.g.: moist, itchy, painful, infectible lesions... "hands-off" treatment.

HARD-TO-TREAT AREAS

e.g.: back, buttocks, limbs; on hirsute areas of chest, genitalia, anus ...easily reaches, evenly covers, effectively penetrates.



formula

METI-DERM Aerosol: Each spray dispenser contains 50 mg. prednisolone. A 3-second spray delivers approximately 0.5 mg., an amount sufficient to cover an area about the size of the hand.

METI-DERM with Neomycin Aerosol: Each spray dispenser contains 50 mg. prednisolone and 50 mg. neomycin sulfate. A 3-second spray delivers approximately 0.5 mg. of prednisolone and 0.5 mg. of neomycin sulfate.

packaging

METI-DERM Aerosol and METI-DERM with Neomycin Aerosol, 150 Gm. spray containers.

also available

METI-DERM Cream 0.5%

METI-DERM Ointment 0.5% with Neomycin

METI-DERM,® brand of prednisolone topical. Meti,® brand of corticosteroids.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

Schering

MD-J-31F

now

FOR VAGINAL MONILIASIS HYVA GENTIAN VIOLET VAGINAL TABLETS

The Only Specific Antimycotic Vaginal Tablet With A Gel Forming Base

A new vaginal therapy specifically designed to produce unmatched and outstanding results. Methylrosaniline chloride (gentian violet) has generally proved the most effective and specific agent for the treatment of vaginal candidiasis caused by the fungus Candida.

Hyva Gentian Violet Tablets virtually eliminate the principal disadvantages of present gentian violet preparations. They may be handled without staining and have psychological and aesthetic acceptance.

Hyva combines the fungicidal action of gentian violet (1.0 mgm.) with three active surface reducing agents and bactericides.* These active ingredients have been incorporated into a mildly effervescent "gel" forming base which provides for maximum and prolonged effectiveness. Shorter treatment time is required without the usual messiness normally experienced.

One tablet intravaginally for 12 nights. When necessary one tablet twice daily may be recommended. Patient should take a Nylmerate Solution water douche on arising and preceding next tablet application.

Prescribe Hyva Gentian Violet Tablets—boxes of 12 tablets.

*Alkyldimethylbenzylammonium chloride (0.5 mgm.)
Polyoxyethylenenonylphenol (10.0 mgm.)
Polyethlene Glycol Tert-Dodecylthioether (5.0 mgm.)

WRITE FOR DESCRIPTIVE LITERATURE

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she can choose her own silver...

but she needs **your** help **in planning her family**

Delfen®
VAGINAL CREAM

THE MODERN CHEMICAL SPERMICIDE

Preceptin®
VAGINAL GEL

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION

IN VAGINITIS...

IN MONILIASIS "...more **EFFECTIVE** than any other agent..."[1]

IN THE MIXED INFECTIONS "...the most **EFFECTIVE** treatment..."[2]

IN TRICHOMONIASIS "...the most **EFFECTIVE** treatment..."[3]

IN TRICHOMONIASIS "...the most **EFFECTIVE** treatment available."[4]

AVC IMPROVED...

1. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 2. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946. 3. Cortese, J. T., and Padovano, L.: J. M. Soc. New Jersey 28:367, 1931. 4. Cortese, J. T.: Clin. Med. 2:45, 1955.

STOPS THE TORMENT

Applied twice daily, AVC Improved
- stops pruritus
- eliminates discharge
- controls irritation and inflammation

DESTROYS THE CAUSE

A synergistic combination of sulfanilamide and 9-aminoacridine, AVC Improved is
- highly effective against Trichomonas, Monilia and the mixed infections
- restores normal acid pH

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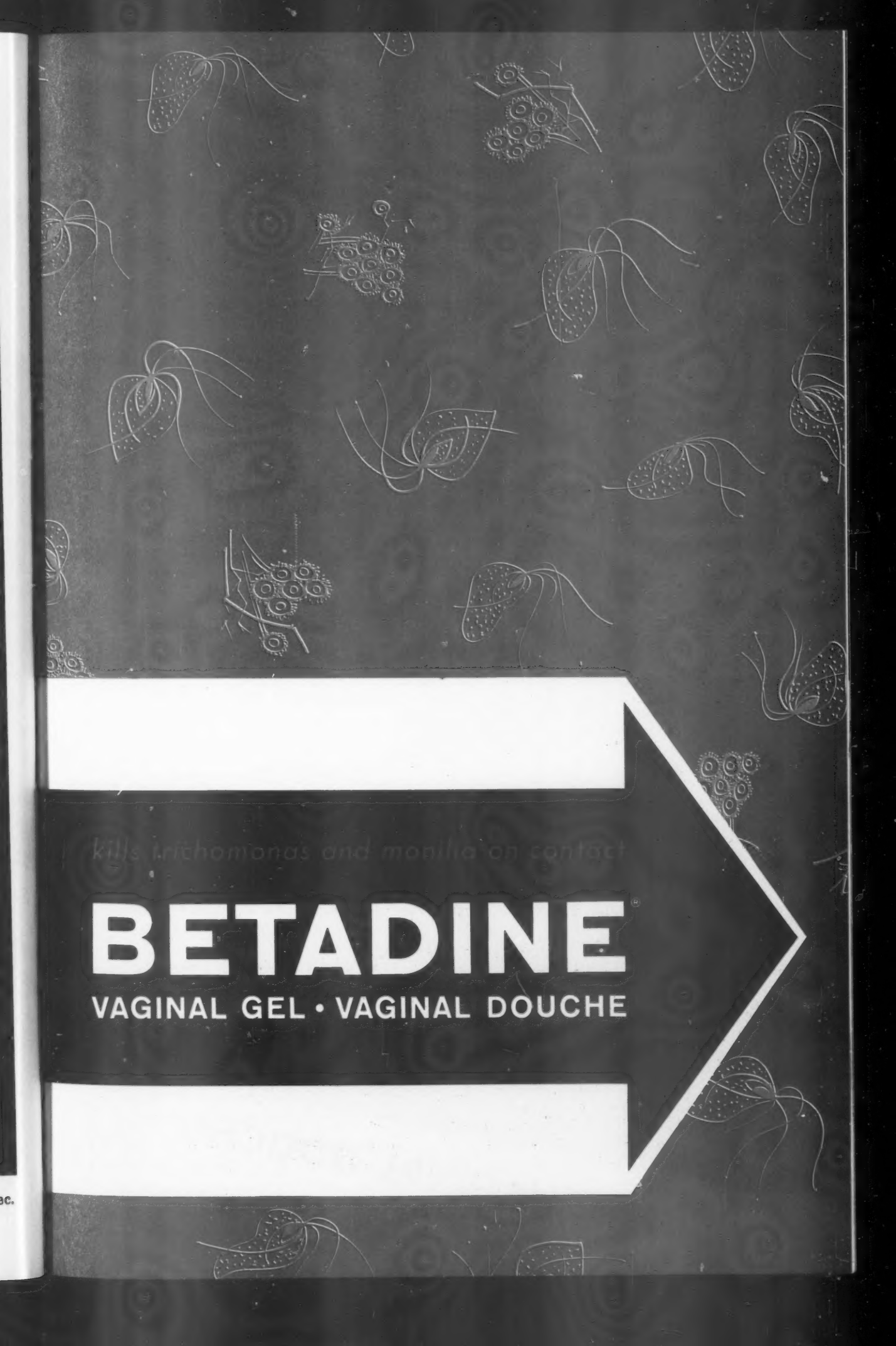
kills trichomonas and monilia on contact
BETADINE®
VAGINAL GEL • VAGINAL DOUCHE

BETADINE

brand of Povidone-Iodine, possesses broad-range germicidal activity against fungi, yeasts, bacteria, protozoa, and viruses. In the vaginal tract Betadine Vaginal Gel and Betadine Vaginal Douche kill trichomonas and monilia on contact and destroy common pathogens. Betadine is virtually nonirritating to vaginal mucosa.

indicated:

in the treatment of trichomoniasis, moniliasis and nonspecific vaginitis.

advantages:

- almost immediate relief from leukorrhea, pruritus; diminishes malodor
- unsurpassed broad-range microbicidal activity
- therapeutically active even in the presence of blood, pus, vaginal secretions
- wetting action to assist penetration into vaginal crypts and crevices

how to use:

In the office: Swab the vaginal vault with Betadine Antiseptic, full strength.

prescribe Betadine Vaginal Douche for therapeutic use as follows: Two (2) tablespoonfuls to a quart of lukewarm water once daily by the patient at home, for six days. On the seventh day, the patient returns for re-examination and swabbing with Betadine Antiseptic; an additional week of therapeutic douching if necessary.

prescribe Betadine Vaginal Gel as follows: Insert one (1) applicatorful of Betadine Vaginal Gel each night, followed by a douche the next morning, through the entire menstrual cycle. If further therapy is warranted, the gel should be continued only during the actual menses days of the following two menstrual periods.

After the infection has been brought under control, the use of Betadine Vaginal Douche is recommended twice weekly at a dilution of one (1) tablespoonful to a quart of lukewarm water.

established in 1905

TAILBY-NASON COMPANY, INC., Dover, Delaware

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3 OZ. TUBE WITH APPLICATOR

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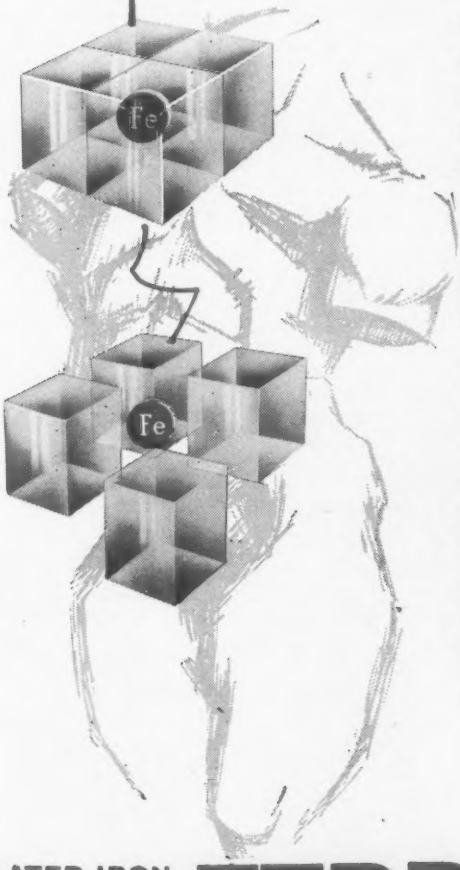

chelate "packaging" protects against iron loss or irritation in transit through g.i. tract **...may be given with meals or ulcer medication without loss of therapeutically available iron... or may be taken on an empty stomach without irritation** *—because chelated iron is not ionized and resists precipitation by alkali, protein, phosphate, or phytate.*

chelate "packaging" ensures physiologic acceptance of iron on delivery to intestinal mucosa... **proved clinically effective in moderate or severe hypochromic anemia[1] yet minimizes risk of toxicity on accidental overdosage**—*because chelation keeps iron in solution over an extended mucosal area for rapid uptake as required, yet inhibits excessive diffusion of iron into the circulation.*

CHELATED IRON
clinically superior in toleration, safety, and physiologic uptake

FERROLIP®
(Iron Choline Citrate†)

TABLETS
SYRUP
PEDIATRIC DROPS

Supplied: FERROLIP TABLETS, SYRUP, and PEDIATRIC DROPS. Daily adult dose of 3 tablets or 1 fl.oz. syrup provides equivalent of 120 mg. elemental iron. Bottles of 100 and 1000 tablets; syrup in pints and gallons. Each cc. of pediatric drops provides 25 mg. elemental iron. In 30-cc. unbreakable plastic squeeze bottles.

Also available: During pregnancy—FERROLIP ob Tablets, chelated iron with vitamin-mineral essentials; phosphorus-free. **For macrocytic and microcytic anemias—FERROLIP plus** (Capsules and Liquid), chelated iron plus other recognized hematopoietic factors.

*CHELATION: "a well-recognized chemical process wherein metallic ions are sequestered and bound into claw-like rings within the chelating molecule... Hemoglobin has long been recognized to be a chelate complex of iron..."[1]

1. Franklin, M. et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, 1958.

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†U. S. PAT. 2,575,611

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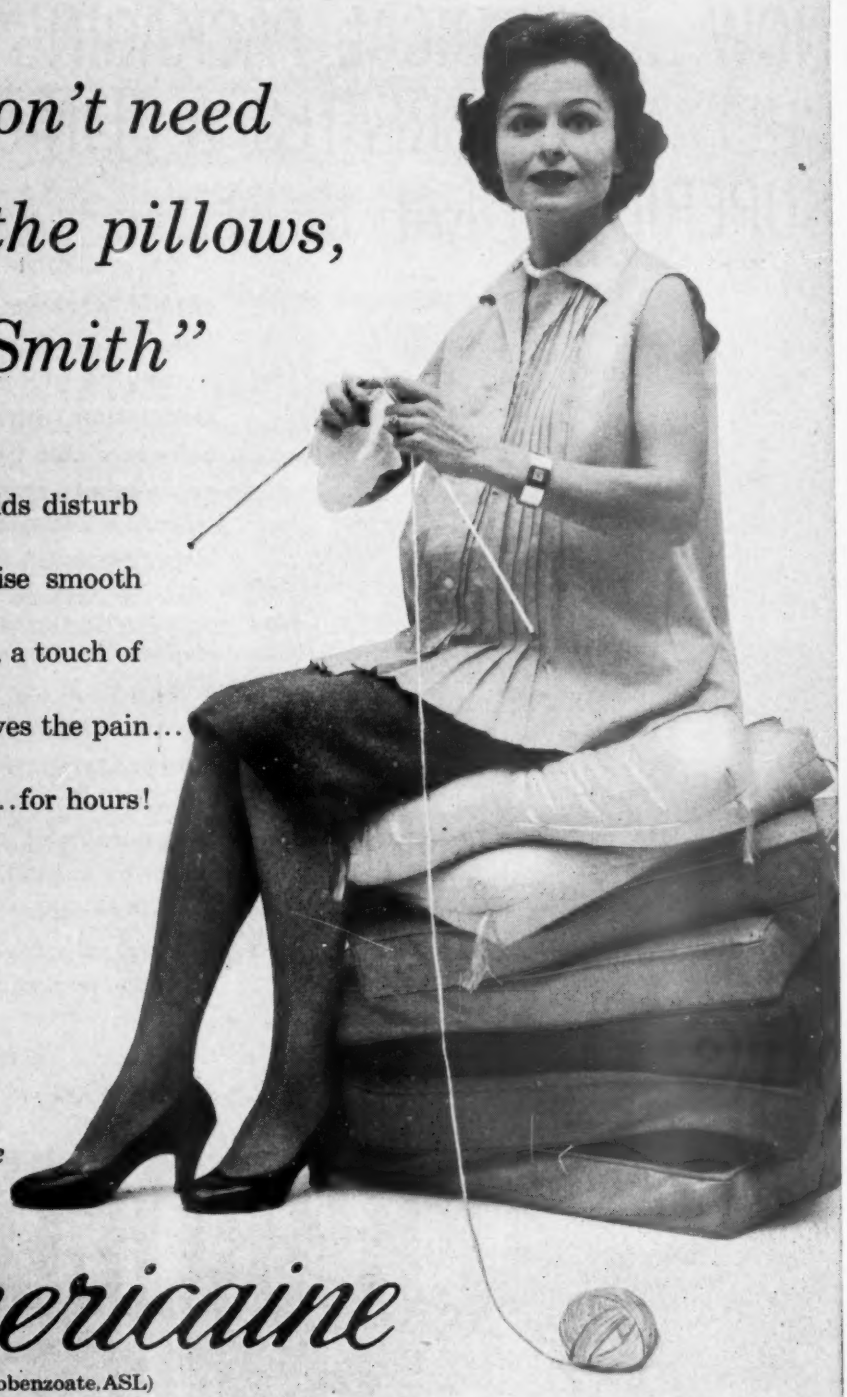

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Nothing relieves surface pain like

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(Ethyl-p-aminobenzoate, ASL)

Topical Anesthetic Ointment and Aerosol

Send for samples

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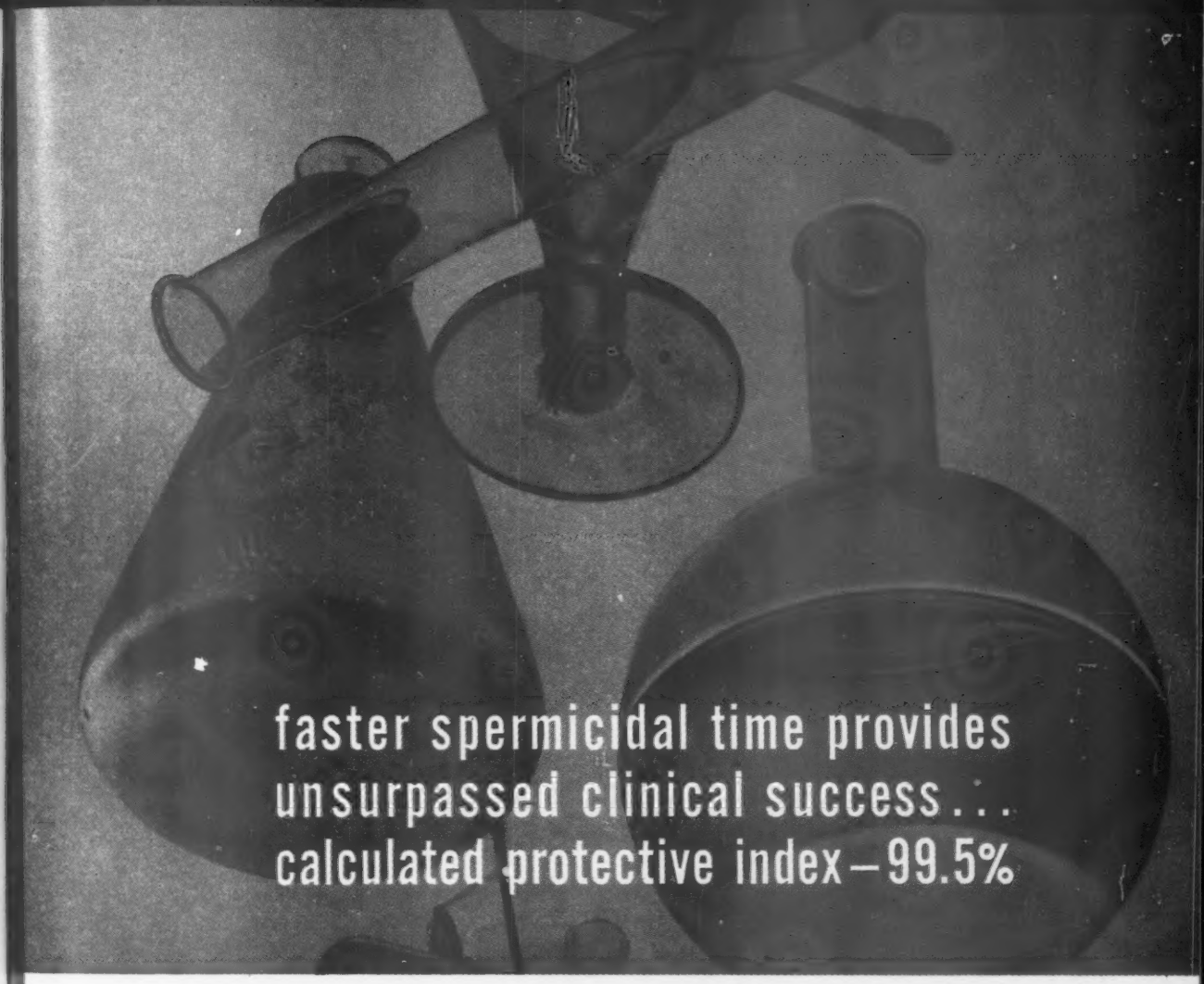

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Protective Index — over 99.5%: In over 200 patient-years' use, by more than 400 women of proven fertility, only one unplanned pregnancy was reported during controlled studies by leading clinics and outstanding private practitioners.[3-6]

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References: 1. Gamble, C. J.: "Diffusion Spermicidal Times of Commercial Contraceptive Jellies and Creams Secured in 1956," Am. Pract. & Digest Treat. (Nov.) 1958. 2. Berberian, D. A., and Slighter, R. G.: Cytometer Chamber Spermatocidal Test, An Improved Technique for Evaluating Spermicidal Activity, J.A.M.A. Clinical Notes *168*:2257 (Dec. 27) 1958. 3. New York City Study: "Interim Report on Clinical Investigation of Lanesta Gel," Personal Communication, To be published on completion. 4. McEvers, J.: "Interim Report on Clinical Investigation of Lanesta Gel," Personal Communication, To be published on completion. 5. West Coast Study I: "Interim Report on Clinical Investigation of Lanesta Gel," Personal Communication, To be published on completion. 6. West Coast Study II: "Interim Report on Clinical Investigation of Lanesta Gel," Personal Communication, To be published on completion. 7. "Definitive Studies of New Spermicides," Research Section, Esta Medical Laboratories, Chicago, Illinois, (June) 1957. 8. Peri, Gisella: "Vaginal Tolerance of Lanesta Gel in Common Leukorrheas," Personal Communication.

LANESTA® GEL, a product of Lanteen® research.

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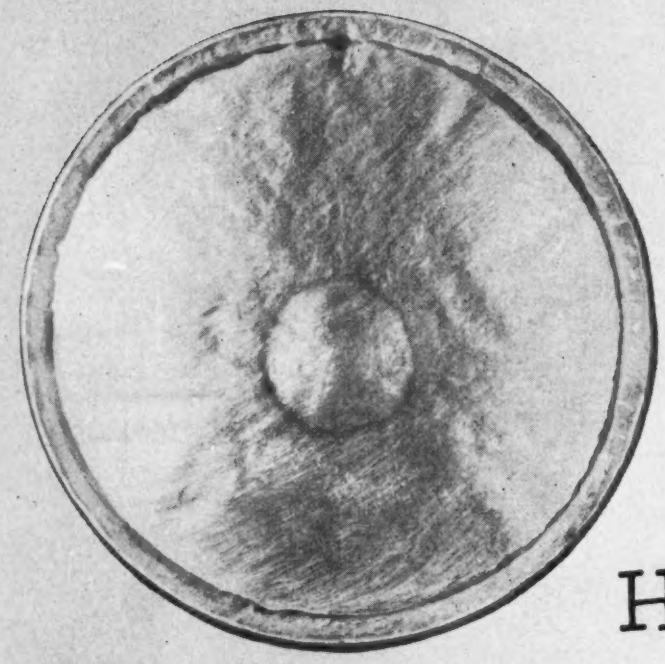

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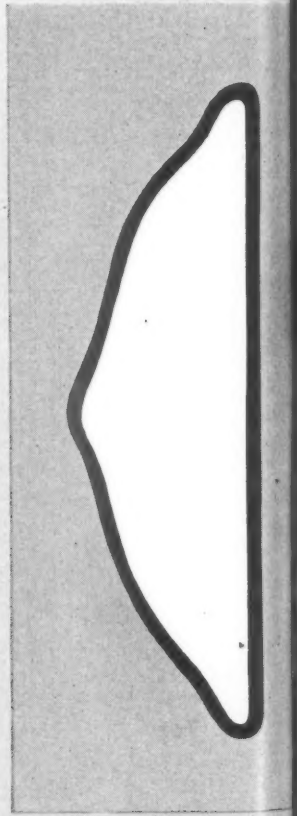

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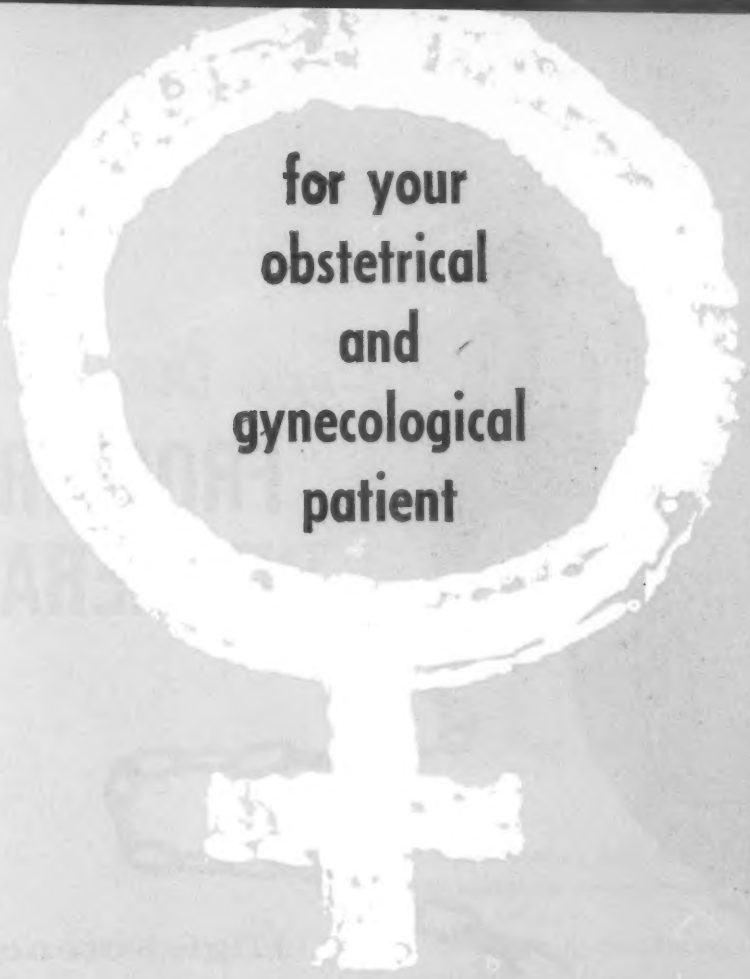

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A single **BACULIN** *vaginal tablet generally destroys the causes of vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe* **BACULIN** *vaginal tablets in your next case of non-venereal vaginitis.*

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Reference: 1. Peña, E. F., Med. Times, 82-921, 1954.

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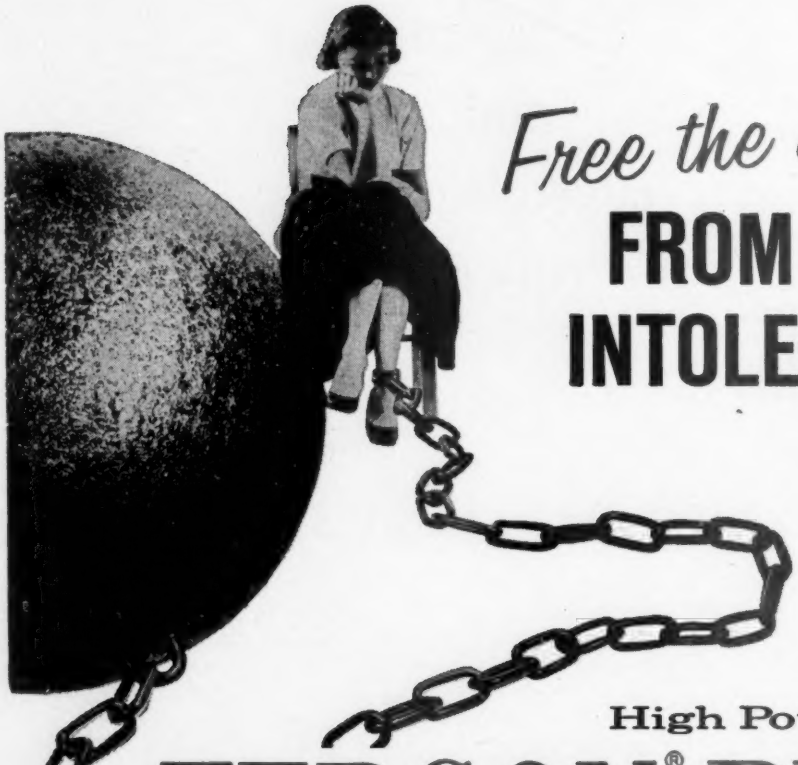

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Fergon (brand of ferrous gluconate) (Iron without Irritation)	1000 mg.
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No Nausea
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in approximately 90% of patients

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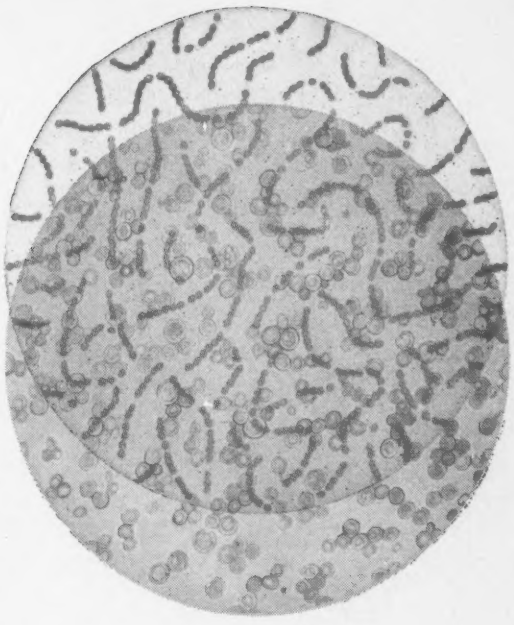

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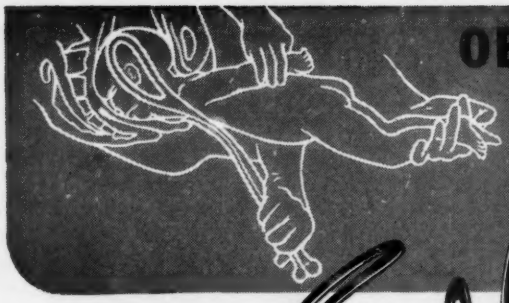

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Standard preoperative procedure to control bleeding

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SALICYLATE

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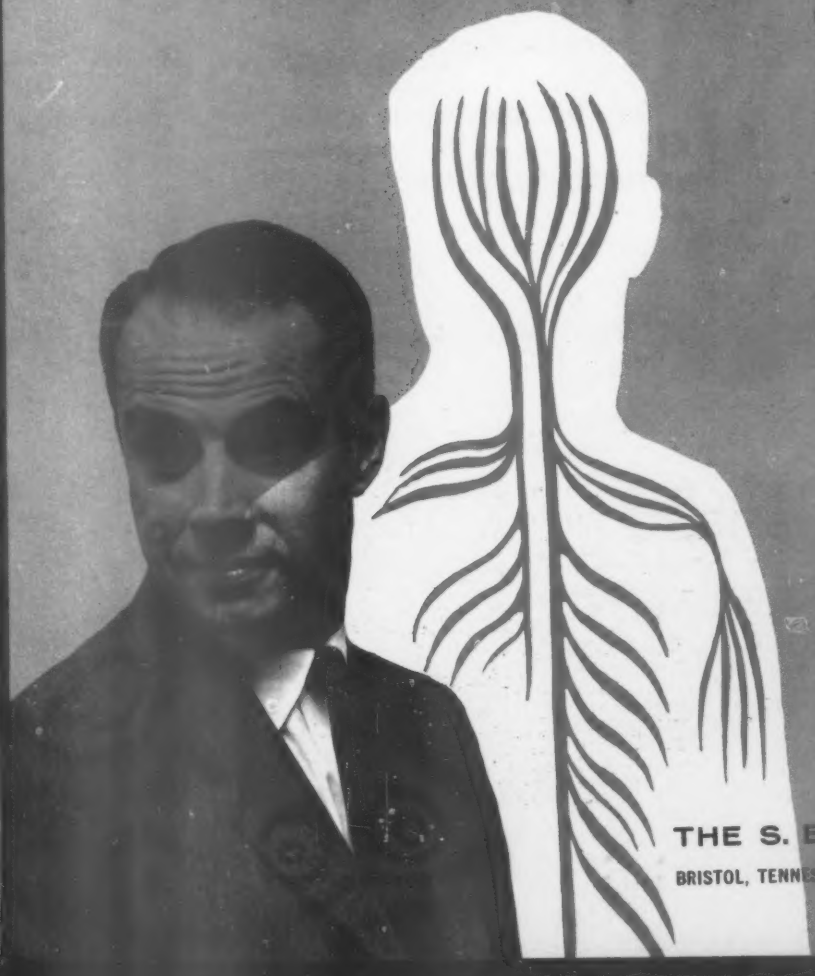

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In hemostasis blood clotting is only one factor. Restoration of capillary integrity is of primary importance.[1-5] Adrenosem controls bleeding and oozing by decreasing excessive capillary permeability and promoting the retraction of severed capillary ends.[1-20]

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Adrenosem is recommended preoperatively where bleeding presents a problem. Minimal bleeding provides a clearer operative field and facilitates operative procedures.[9-20,23] Postoperatively, it lessens the need for transfused blood.[3,6,9-11,13,16,18,20,23]

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Adrenosem is an effective hemostatic where vascular anomalies exist, such as telangiectasia, purpuras, epistaxis, and others.[1-3,6,9-11,27-29] At recommended dosage levels there are no contraindications.

Supplied: Ampuls, 1 cc., 5 mg.; Tablets, 1 and 2.5 mg.; Syrup, each 5 cc., 2.5 mg. Potency of all dosage forms is stated in terms of the active ingredient, adrenochrome monosemicarbazone.

Write for descriptive literature and dosage schedules

*U. S. Pat. 2581850, 2506294

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(Brand of carbazochrome salicylate)

effective in more than 200 clinical disorders

Adrenosem has proved effective, both prophylactically and therapeutically, in numerous operative procedures and pathological conditions. Following is a partial list of the many indications for Adrenosem.

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hy *pericardiorrhaphy* **splenectomy** *stomatoplasty* **cheiloplasty** *uvulectomy*

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traction *skin grafts* **scar excisions** *dermabrasion* **gastrointestinal bleed**

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on capillary hemorrhage during hedulin, dicumerol or x-ray thera

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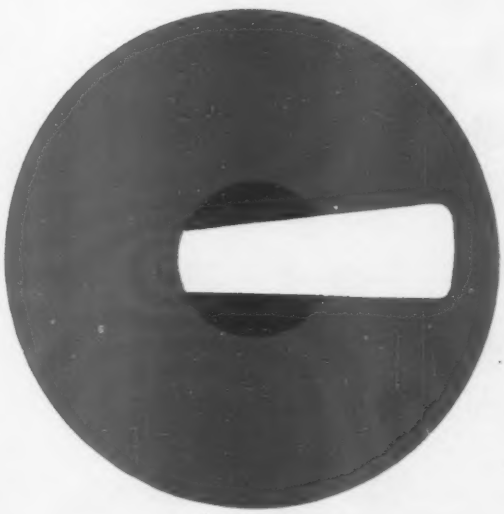

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Gilliotte, B. W.: Clin. Med. 6:223, 1959

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▪ provide adequate antibacterial concentrations at hard-to-reach sites of infection ▪ relieve local pain and discomfort ▪ slender, tapered shape permits easy introduction

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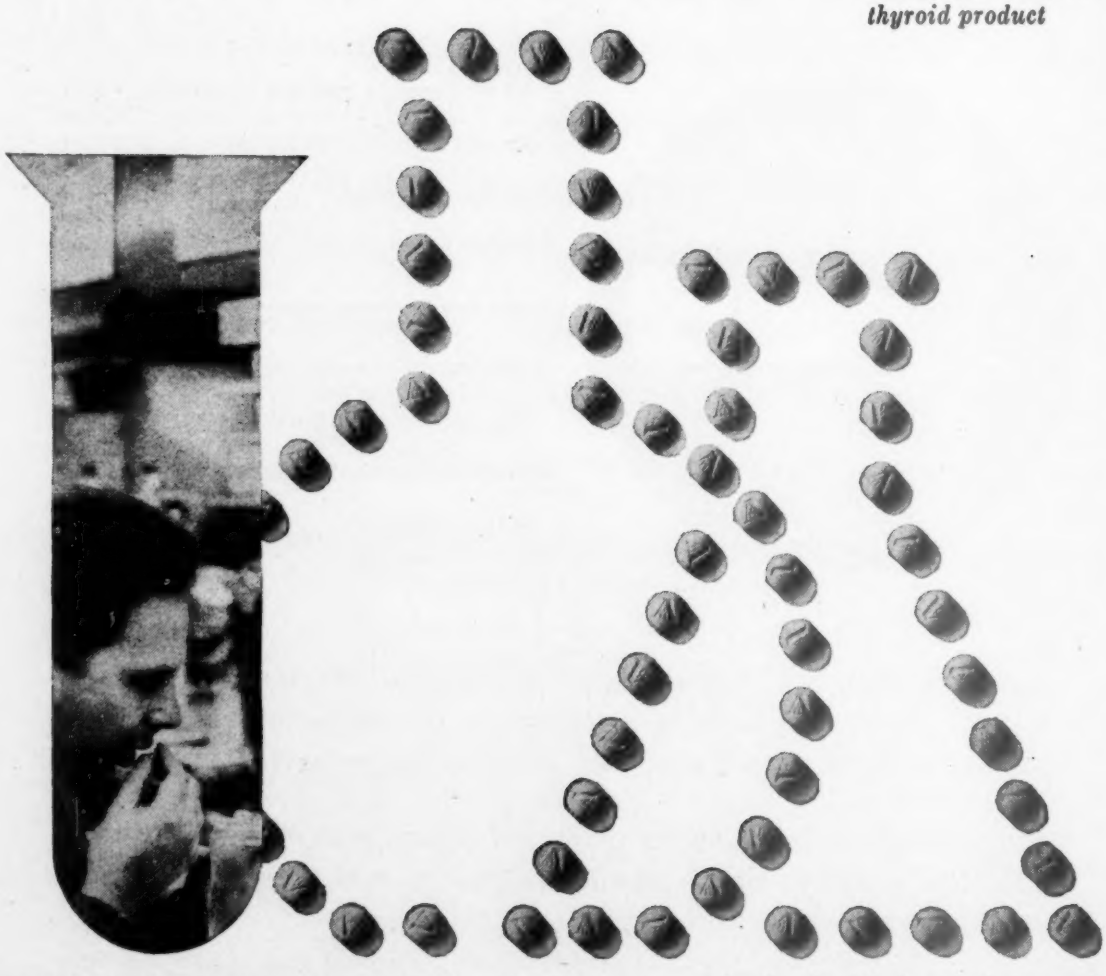

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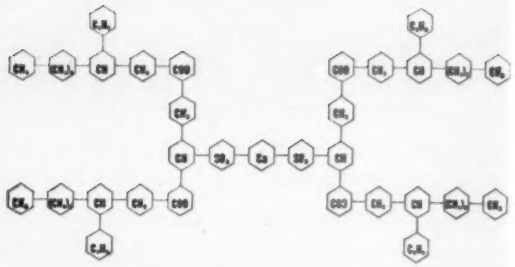
DESITIN SUPPOSITORIES lubricate, soothe, protect, ease pain, itching . . . and aid healing (with Norwegian cod liver oil, rich in vitamins A and D and unsaturated fatty acids). Free from drugs which might mask serious rectal disease.

Write for samples and literature[1-3]

DESITIN CHEMICAL COMPANY

812 Branch Ave., Providence 4, R. I.

NEW THERAPEUTIC CHEMICAL IN CONSTIPATION



Calcium Bis-(Dioctyl Sulfosuccinate)

The discovery by Wilson and Dickinson[1] at the University of Michigan that dioctyl sodium sulfosuccinate could correct constipation through fecal softening action marked a real advance in therapy. In cases of unimpaired bowel motility this new physico-chemical principle presented a new means of correcting bowel dysfunction without the need of catharsis.

Continuing research has now led to the development of a new therapeutic surfactant with more than double the surfactant effectiveness of the original dioctyl sodium sulfosuccinate.

This new substance, calcium bis-(dioctyl sulfosuccinate), reduces interfacial tension to a minimal value at a concentration of only 0.035 per cent. A minimal value of this order in dynes per centimeter requires 0.1 per cent or more of the older dioctyl sodium sulfosuccinate.

INTERFACIAL TENSION (Oil-Water Interface) *Calcium Bis-(Dioctyl Sulfosuccinate)*	
Dynes/cm.	**Concentration**
55.0	0.00%
13.3	0.01%
9.9	0.02%
8.4	0.03%
7.4	0.035%

Improved homogenization of the immiscible lipoid and aqueous phases of the intestinal content depends upon maximum reduction of interfacial tension. The greatest degree of fecal softening is achieved with surfactant agents capable of reducing interfacial tension to minimal values. Calcium bis-(dioctyl sulfosuccinate) represents a markedly more effective surfactant agent since maximum surfactancy results from less than half the concentration of previously used surfactants.

DOSAGE:

DOXICAL 240 mg. SOFT GELATIN CAPSULES — *for adults, one daily.*

DOXICAL 50 mg. SOFT GELATIN CAPSULES — *for children and adults with minimum needs, one to three daily.*

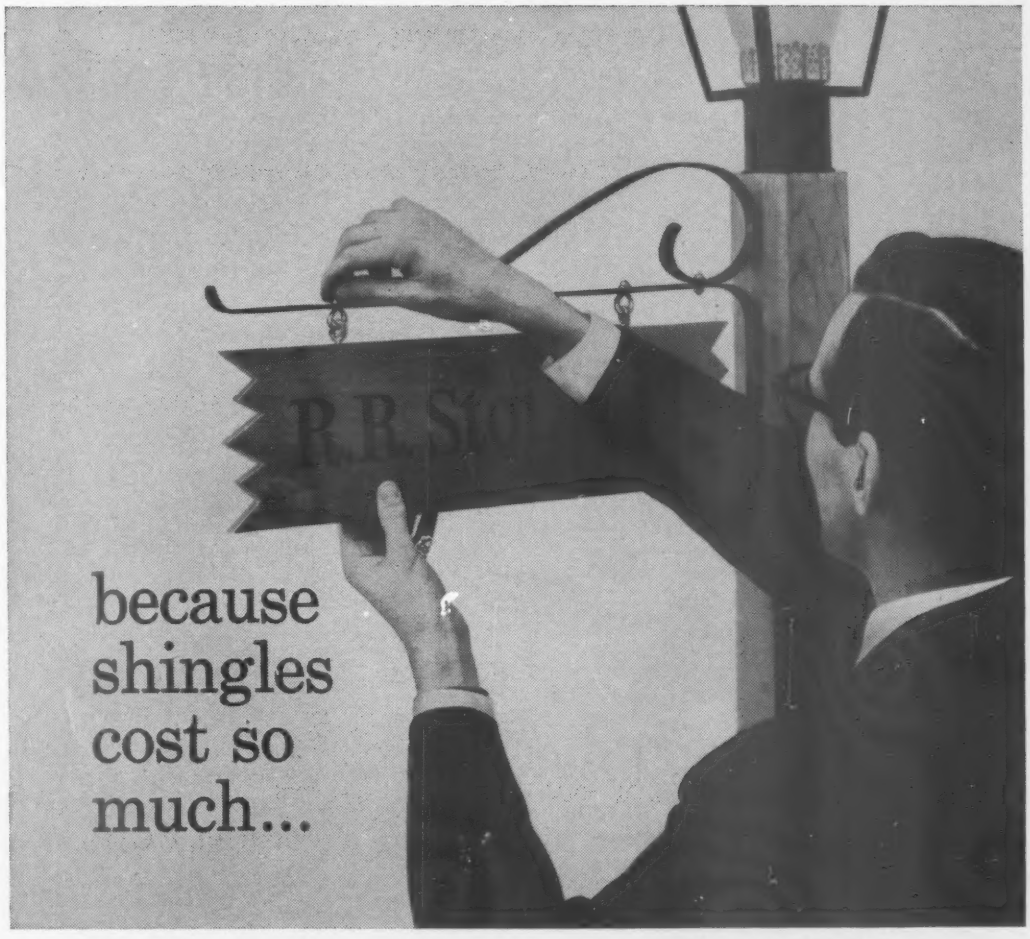
1. Wilson, J. L., and Dickinson, D. G.: J.A.M.A. 158:261-263 (May 28) 1955.

This new chemical, definitely superior in surfactant action, is indicated in the treatment of chronic constipation where non-laxative fecal softening therapy is the preferred regimen.

The usual adult dose is 240 mg. daily. For children and adults with minimum needs, 50 to 150 mg. daily may be given.

DOXICAL

LLOYD BROTHERS, INC. **CINCINNATI 3, OHIO**



you need the protection of **TRUE SECURITY**

Few men have to spend many thousands of dollars for equipment just to get started, as you probably did. And this is only one of the unusual financial hurdles in a medical career. It takes wise planning to meet these special problems and at the same time provide for your family's protection.

Financial planning for medical men has been a specialty of Mutual Benefit Life for over a century. Mutual Benefit Life can give you a comprehensive solution to your particular problems with a personally designed and economical plan for your TRUE SECURITY.

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THE MUTUAL BENEFIT LIFE INSURANCE COMPANY
AGENCY DEPT. AOG-2
NEWARK 1, NEW JERSEY

Name.....

Address.....

City.....State.....

quick, accurate early pregnancy diagnosis...

new, 3-day oral test for pregnancy

Pro-Duosterone®

anhydrohydroxyprogesterone 50.00 mg.
activated by ethinyl estradiol 0.03 mg. } per tablet

safe . . . physiologic . . . therapeutic

Pregnancy may now be diagnosed safely, simply and accurately in its earliest weeks by oral administration of PRO-DUOSTERONE® tablets four times daily—with each meal and at bedtime—for only three consecutive days. In the nonpregnant patient uterine bleeding usually occurs 3 to 7 days after progesterone therapy.[1] No bleeding occurs when pregnancy exists; on the contrary, gestation is protected.[2] Moreover, in short-term functional amenorrhea regular menstrual cycles are usually restored by oral progestogen.[1]

The speed and precision of this oral diagnostic test are unsurpassed, and "no laboratory equipment, animals, or specimens are needed."[1] The 3-day, oral PRO-DUOSTERONE test for pregnancy is also less costly than biologic methods. Finally, full diagnostic and therapeutic efficiency is assured by the small estrogen component of the PRO-DUOSTERONE formula since "Progesterone has no action whatsoever in the absence of estrogens."[3] Supplied: Bottles of 24 pink tablets. **Roussel Corporation,** 155 E. 44th St., New York 17

1. Hayden, G. E.: Am. J. Obs. & Gynec. 76:271, 1958. 2. New & Nonofficial Drugs: J.A.M.A. *168*:181, 1958. 3. Page, E. W.: GP 9:53, 1954.

"Premarin"
Vaginal Cream

promotes proliferation and
vascularity of the vaginal mucosa in
postmenopausal patients, and used

pre- and postoperatively

tends to restore the integrity
of atrophied, friable tissues, and
change the vaginal environment to one
that resists infection, which

facilitates surgery—favors healing

Applied for 7 to 10 days before, and for 10 days after plastic vaginal surgery in the postmenopausal patient, "Premarin" Vaginal Cream effectively revitalizes the vaginal epithelium making the intervention less difficult and accelerating healing. It is also widely prescribed for the prompt relief of senile vaginitis and pruritus vulvae, as well as juvenile vaginitis. Also available with hydrocortisone as "Premarin" H-C Vaginal Cream for use when immediate anti-inflammatory, antipruritic action is indicated, particularly in the initial stages of estrogen therapy of various vulvovaginal disorders.

"Premarin"® conjugated estrogens (equine) AYERST LABORATORIES, New York 16, N.Y.; Montreal, Canada

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faster recovery, greater comfort for your OB-GYN patients

Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, FURACIN CREAM promptly controls infection; reduces discharge, irritation and malodor; hastens healing. FURACIN CREAM is active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

FURACIN® CREAM

BRAND OF NITROFURAZONE

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator. Also available: FURACIN Vaginal Suppositories.

THE NITROFURANS—a *unique* class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

From all over America

HOSPITAL STAFFS ACCLAIM 'SENOKOT' IN THE TREATMENT OF CONSTIPATION

'Senokot' Tablets and Granules are routinely prescribed in more than 3000 hospitals from coast to coast and overseas. 'Senokot' is preferred, not only by hospitals, but by an ever-growing number of physicians for the safe, physiological correction of constipation. Following are typical comments, among many, from hospitals throughout the United States:

CHARLOTTE, NORTH CAROLINA

"...not one of the patients has experienced any untoward reaction nor has there been any evidence of diarrhea in the infants of post-partum mothers who were breast feeding."

"...nurses...report that they no longer have complaints of abdominal 'griping' pain which was so prevalent heretofore with the usage of harsher laxatives in post-partum patients."[1]

BERWYN, ILLINOIS

"...standard item in the obstetrical service at MacNeal Memorial Hospital."[2]

SCHENECTADY, NEW YORK

"Definitely it cuts down on the amount of postpartum nursing care from a point of view of giving postpartum enemas. For this, the nurses are very thankful."[3]

GALVESTON, TEXAS

"...very helpful in the postoperative care of our patients..."[4]

NORRISTOWN, PENNSYLVANIA

"...have been used mainly with patients who complained of constipation as a side effect of chlorpromazine therapy."[5]

BATTLE CREEK, MICHIGAN

"...we are using Senokot more frequently than any other product in its class for mild constipation..."[6]

BOSTON, MASSACHUSETTS

"...certainly effective clinically..."[7]

PHOENIX, ARIZONA

"...cut down the number of enemas required by approximately 60 per cent..."[8]

PHILADELPHIA, PENNSYLVANIA

"Undoubtedly it does reduce the nurses' time and efforts, particularly in that few enemas are required..."[9]

MINNEAPOLIS, MINNESOTA

"...clinically effective...has reduced post-partum enemas at least two-thirds."[10]

AKRON, OHIO

"...very effective and helpful; the nurses are particularly happy to have a product such as yours. No untoward accidents have occurred thus far on our service..."[11]

TYLER, TEXAS

"It reduces the nurses' time, and we do recommend it for our patients."[12]

CHICAGO, ILLINOIS

"...unquestionably it has reduced the instances of enemas in our Institution."[13]

COLUMBUS, OHIO

"...we are recommending it for our patients."[14]

CITED REFERENCES: 1. Tart, J. M., Jr.: Personal Communication, 1957. 2. Sykora, L. J.: Personal Communication, 1957. 3. Phillips, J. B.: Personal Communication, 1957. 4. McGivney, J.: Personal Communication, 1957. 5. Kremens, J. B.: Personal Communication, 1957. 6. Holsted, E.: Personal Communication, 1957. 7. Abrams, A. A.: Personal Communication, 1958. 8. Van Epps, C.: Personal Communication, 1957. 9. Gruber, F. E.: Personal Communication, 1957. 10. Bergquist, J. R.: Personal Communication, 1957. 11. Wentsler, N. E.: Personal Communication, 1957. 12. Pummer, L. R.: Personal Communication, 1957. 13. Hawkins, R.: Personal Communication, 1957. 14. Baldridge, R. W.: Personal Communication, 1957.

FOR ALL PATIENTS WHO ARE CONSTIPATED - WHATEVER THE FUNCTIONAL CAUSE

natural bowel corrective

Senokot®

TABLETS / GRANULES

SUPPLIED: Granules: Cocoa flavored, in 8 and 4 ounce containers. Tablets: Small and easy to swallow, in bottles of 100.

THE EFFECTIVENESS AND SAFETY OF SENOKOT CONTINUE TO BE DOCUMENTED BY CLINICAL AND LABORATORY INVESTIGATIONS WHICH CONSTITUTE THE FASTEST GROWING BIBLIOGRAPHY ON CONSTIPATION CORRECTION.

The Purdue Frederick Company DEDICATED TO PHYSICIAN AND PATIENT SINCE 1892 NEW YORK 14, N.Y. TORONTO 1, ONTARIO

Eradicate Infection and Restore Normal Vaginal Flora...

New-'Neosporin'® brand Vaginal Suppositories

Trichomonacidal · Bactericidal

Each suppository contains:

'Aerosporin'® brand Polymyxin B Sulfate	**20,000 Units**
Neomycin Sulfate	**5 mg.**
Acetarsone	**250 mg.**
Beta-lactose	**q.s. (approx. 1 Gm.)**

In a base containing a surface active agent
Foil-wrapped—Box of 12

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

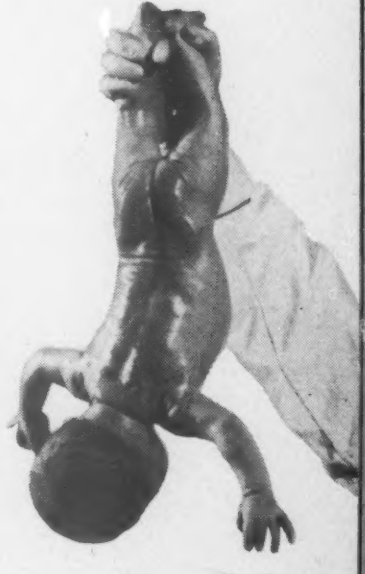
Report on more than 8200 cases of obstetrical sedation

"... *it is rare to hear a patient cry out*

even at the peak of the contractions"[1]

Published analysis[1,2] of the records of thousands of patients shows these typical results of the PHENERGAN regimen: *Mothers* are relieved of fear. "The . . . labor room is noticeably quieter. . . ."[1] Patients arrive in the delivery room mentally clear and cooperative. Antepartum, intrapartum, and postpartum nausea and vomiting are sharply decreased. Induction of and emergence from general anesthesia are smooth. Because PHENERGAN potentiates anesthetics, barbiturates, and narcotic analgesics, there is reduced need for these agents. *Infants* usually cry spontaneously, without evidence of respiratory depression. *Side-effects* seldom interfere with use.

1. Carroll, J.J., and Moir, R.S.: J.A.M.A. *168*:2218 (Dec. 17) 1958.
2. Adelman, M.H., et al.: J.A.M.A. *169*:5 (Jan. 3) 1959.



"... the infants ... showed good muscle tone and cried immediately on delivery or within 60 seconds. . . ."[2]

PHENERGAN®

HYDROCHLORIDE

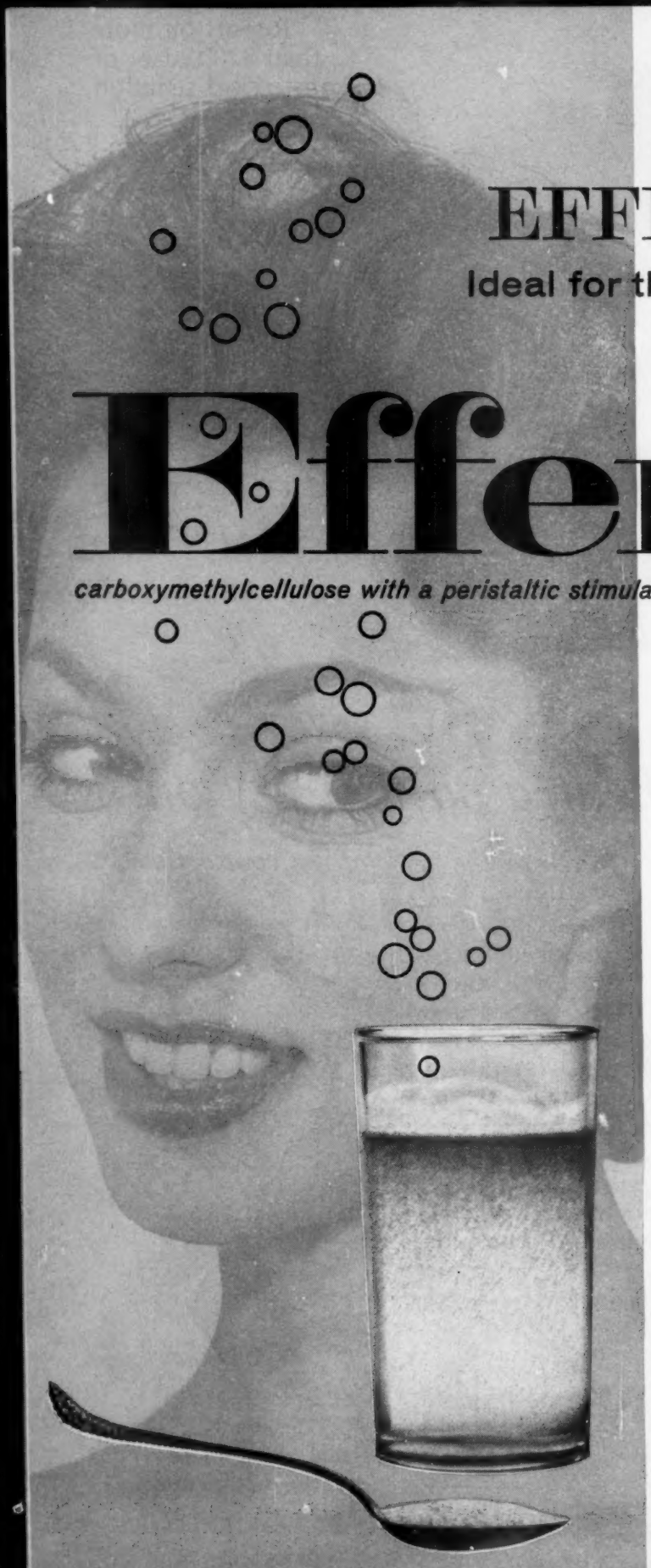
Promethazine Hydrochloride, Wyeth

INJECTION • TABLETS • SYRUP • SUPPOSITORIES

Wyeth®

Philadelphia 1, Pa.

Emerging as a drug of choice in field after field of medicine



2 EFFERVESCENT

Ideal for the range of constipation from childhood

Effergel

carboxymethylcellulose with a peristaltic stimulant

BETTER RESULTS

- produces natural, soft, well-formed stools.
- lubricating, non-irritating bulk, low-in-sodium.
- greater hydrophilic capacity... gelling takes place in the intestine, not in the stomach.
- mild peristaltic stimulation assures predictable results.

MORE FLEXIBLE

- granular powder form allows infinite dosage variation for the full range of constipation... occasional to obstinate... from childhood to geriatric.

EFFERVESCENT

- easy-to-take... really tastes good, lemon-flavored.

CONTENTS:

Each 7 Gm. white granular powder *(approximately 1 rounded teaspoonful)* provides:

Sodium Carboxymethylcellulose ..... 2 Gm

Di(acetylhydroxyphenyl)isatin..... 6 mg.

Stuart

THE STUART COMPANY
PASADENA, CALIFORNIA

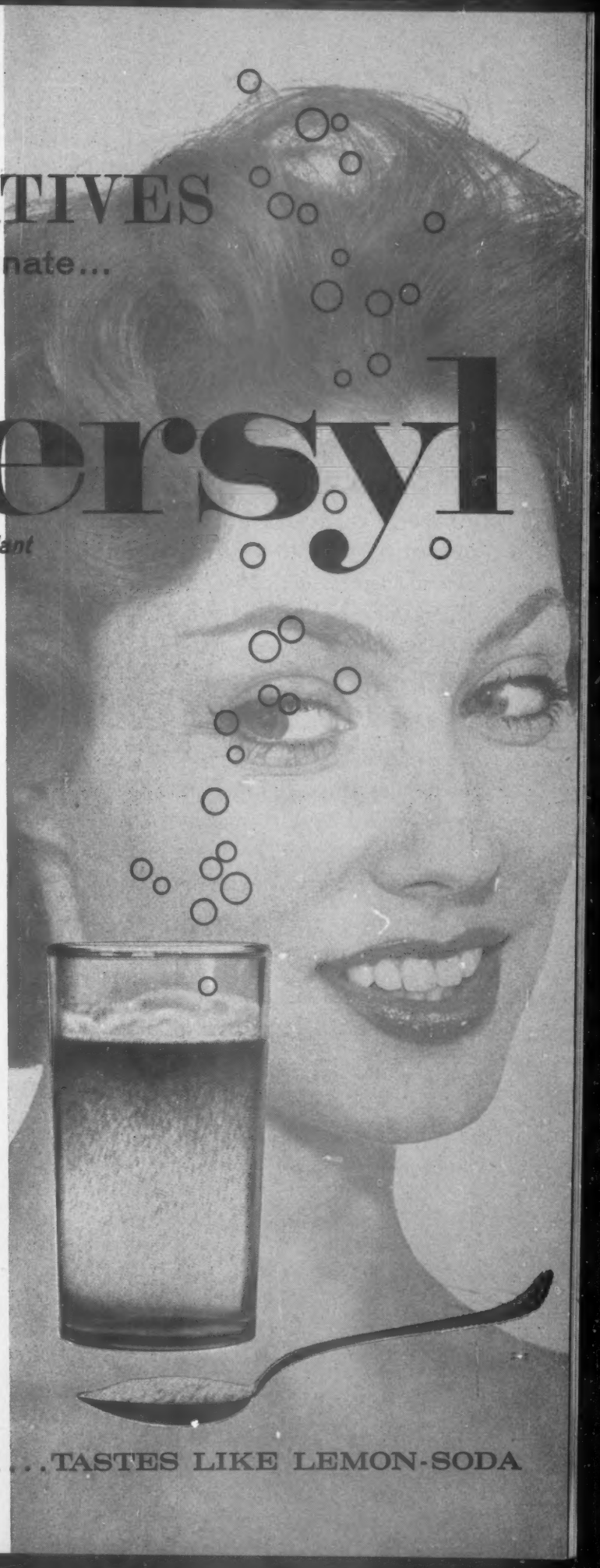
CLEAR, PLEASING, DELIGHTFULLY REFRESHING

NEW BULK LAXATIVES

from occasional to obstinate... to geriatric

Effersyl

psyllium with a mild peristaltic stimulant



BETTER RESULTS

- more soft, lubricating bulk and milder peristaltic stimulation combine to produce soft, formed stools.
- sodium-free, non-irritating.

MORE FLEXIBLE

- granular powder form allows infinite dosage variation for the full range of constipation... occasional to obstinate... from childhood to geriatric.

EFFERVESCENT

- easy-to-take... really tastes good, lemon-flavored.

CONTENTS:

Each 7 Gm. pink granular powder *(approximately 1 rounded teaspoonful)* provides:

Psyllium hydrocolloid ..... 3 Gm.
the highly purified hemicellulose of the husk of the psyllium seed. (Plantago ovata, Forsk)

Di(acetylhydroxyphenyl)isatin ..... 3 mg.

DOSAGE – BOTH EFFERGEL AND EFFERSYL:

Adults: initially, 1 rounded teaspoonful in a glass of water, morning and night. Dosage may be increased or decreased to suit needs.

Children 3 years and over: initially, 1 level teaspoonful in one-half glass of water upon retiring. Subsequent dosage to be adjusted according to results.

Availability: 4-ounce and 9-ounce bottles at all pharmacies.

Write for generous tasting samples.

EFFERVESCENT DRINK...TASTES LIKE LEMON-SODA

in childbirth . . .

'Thorazine' as adjunctive therapy has three advantages

1. helps you establish optimum levels of analgesia

   In labor, 'Thorazine' reduces the tension and anxiety which intensify pain, without affecting natural uterine contractions. With 'Thorazine' therapy, the patient in labor is calm, cooperative and responds to pain only mildly.

2. minimizes risk of respiratory depression

   During delivery, because of Thorazine's potentiating effect, the amount of analgesic agents needed is greatly reduced. Thus, the risk of respiratory depression is minimized for both the mother and the infant.

3. controls nausea and vomiting

   In all three stages of childbirth, with 'Thorazine' the incidence of nausea and vomiting is markedly reduced.

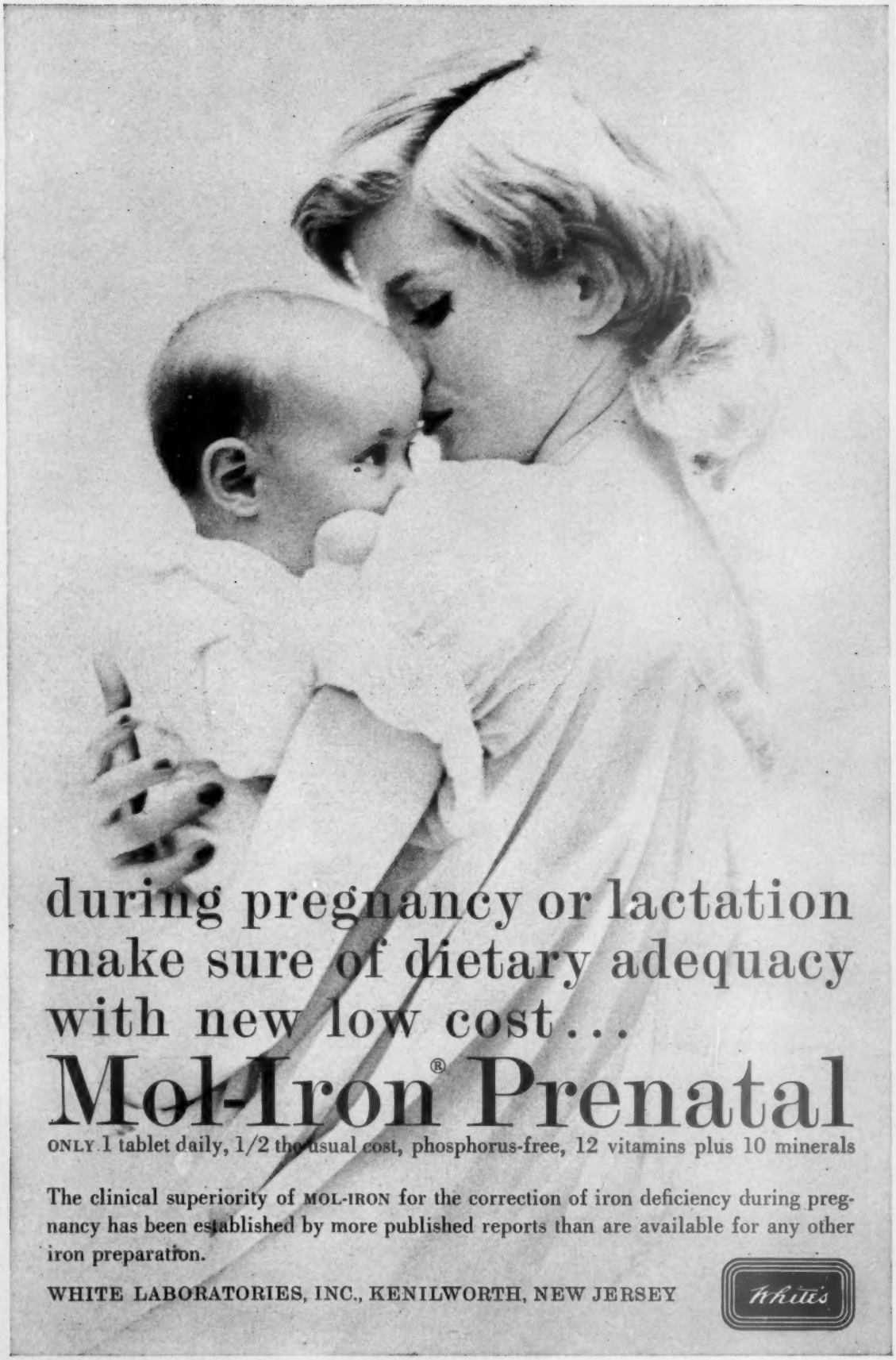
THORAZINE*

chlorpromazine, S.K.F.

one of the fundamental drugs in medicine

SKF Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off.



during pregnancy or lactation
make sure of dietary adequacy
with new low cost...

Mol-Iron® Prenatal

ONLY 1 tablet daily, 1/2 the usual cost, phosphorus-free, 12 vitamins plus 10 minerals

The clinical superiority of MOL-IRON for the correction of iron deficiency during pregnancy has been established by more published reports than are available for any other iron preparation.

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

White's

diagnosis
without
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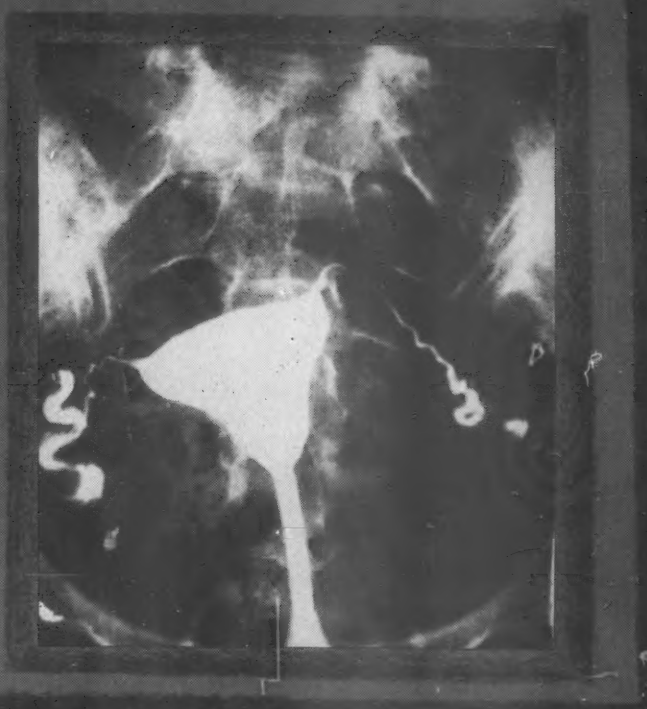

Salpix®
contrast medium

in hysterosalpingography
for detecting uterine
and tubal abnormalities

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Ortho

BONA

BONADOXIN Tablets relieve nausea and vomiting of pregnancy in 9 out of 10,[1-7] often within a few hours.

A controlled study of 620 cases reported that with BONADOXIN "toxicity and intolerance [are] zero."[1] BONADOXIN is rarely soporific. It is free from the risks associated with overpotent tranquilizer-antinauseants.

NOTE: BONADOXIN has also been shown highly effective in relieving nausea and vomiting associated with: anesthesia, radiation sickness, Meniere's syndrome, labyrinthitis, cerebral arteriosclerosis and motion sickness.

Each tiny pink-and-blue BONADOXIN tablet contains:

Meclizine HCl (25 mg.) . . . for antivertiginous, antinauseant effects.

Pyridoxine HCl (50 mg.) . . . for specific metabolic replacement.

DOSAGE: usually one tablet at bedtime. Severe cases may require another dose on arising.

SUPPLIED: tiny pink-and-blue tablets, bottles of 25 and 100. Fruit-flavored, clear green syrup in 30 cc. dropper bottles.

Infant colic? BONADOXIN DROPS are antispasmodic . . . stop colic in 84%,[8-10] without the risk of belladonna and barbiturates.

Each cc. contains:
Meclizine dihydrochloride ..... 8.33 mg.
Pyridoxine hydrochloride ..... 16.67 mg.

Dosage:

under 6 months	0.5 cc.	2 or 3 times daily, on the tongue, in fruit juice or water
6 months to 2 years	1.5 to 2 cc.	
2 to 6 years	3 cc.	
adults and children over 6	1 tsp. (5 cc.)	

References: 1. Goldsmith, J. W.: Minnesota Med. 40:99 (Feb.) 1957. 2. Groskloss, H. H., et al.: Clin. Med. 2:885 (Sept.) 1955. 3. Weinberg, A., and Werner, W. E. F.: Am. Pract. & Digest Treat. 6:580 (April) 1955. 4. Crawley, C. R.: West. J. Surg. 8:463 (Aug.) 1956. 5. Tartikoff, G.: Clin. Med. 3:223 (March) 1956. 6. Dunn, R. D., and Fox, L. P.: Clinical exhibit. 7. Codling, J. W., and Lowden, R. J.: Northwest Med. 57:331 (March) 1958. 8. Dougan, H. T.: Personal communication. 9. Leonard, C. L.: Personal communication. 10. Steinberg, C. L.: Personal communication.

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(tablets and drops)

STOPS

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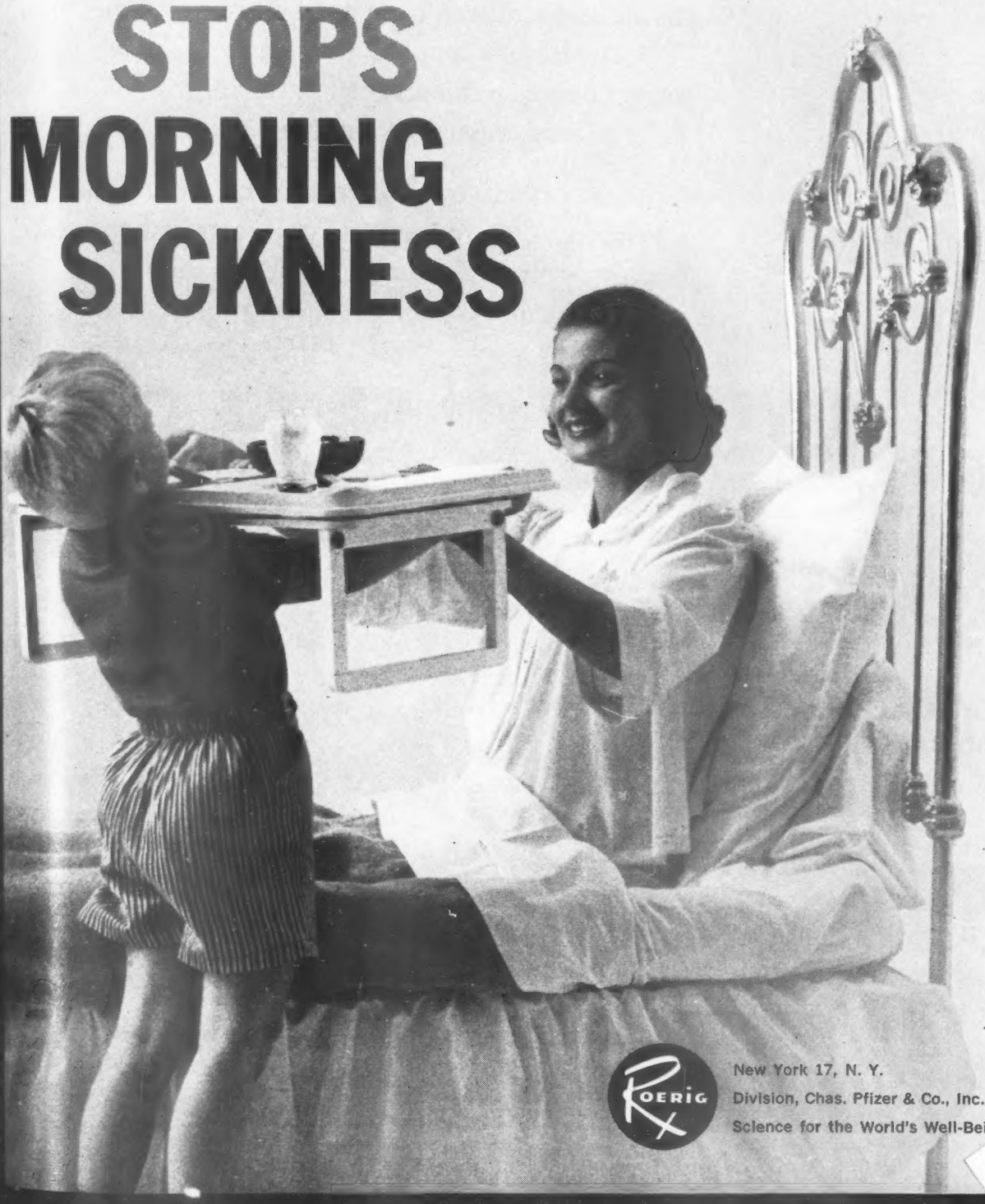
MORNING SICKNESS



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Science for the World's Well-Being

smoothly

confidently

comfortably through estrogen deficiencies

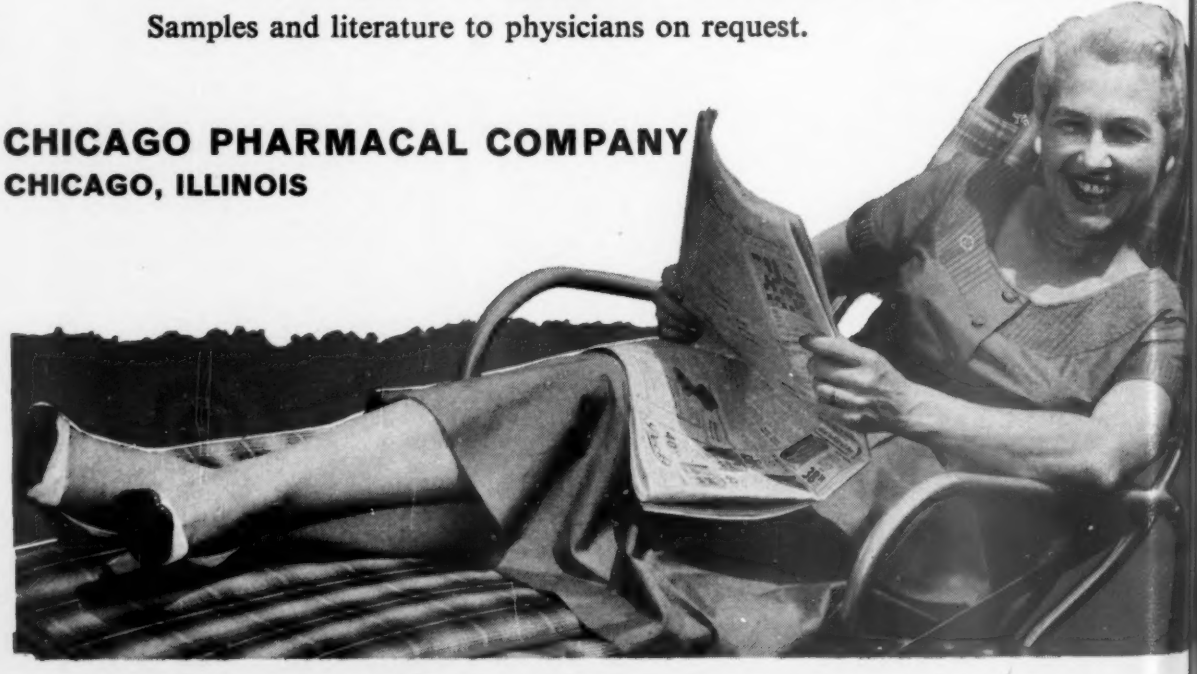
- Simple oral dosage form, plus welcome symptomatic relief through the menopausal period commend ESTROSED therapy to both physician and patient.
- The clinically proved benefits of ethinyl estradiol and reserpine are supplied in a single tablet . . . to correct estrogen imbalance . . . to control accompanying emotional instability.
- For safe, effective management of menopausal patients . . . for potent, well-tolerated estrogen therapy . . . for safe tranquilization . . . for convenient, economical medication, prescribe

estrosed

indications: hypo-ovarianism, menometrorrhagia, postmenopausal therapy. **dosage:** 1 or 2 tablets, two or three times a day, according to symptoms. **supplied:** bottles of 100 and 1000 tablets.

Samples and literature to physicians on request.

CHICAGO PHARMACAL COMPANY
CHICAGO, ILLINOIS



AC-359M

even in drug-induced constipation...

Peri-Colace®

dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

provides predictable, yet gentle, peristaltic stimulation

"It appears that there are at least two components in the total action of Peristim [®*]: (a) a reflex independent peristaltic-stimulating effect and, (b) a fecal-hydrating action which proceeds in spite of ganglionic block or intensive anticholinergic treatment."[1]

effective even in hospitalized patients where bowel motility is depressed . . .

Peri-Colace was administered to 130 hospitalized patients. "The results were almost uniformly good."[2] (Treatment with Peri-Colace was effective in 97% of the patients studied.)

Peri-Colace predictably stimulates gentle peristalsis, moistens and softens stools.

Available in small, soft-gelatin capsules or pleasant-tasting syrup.

*standardized preparation of anthraquinone derivatives from cascara sagrada, Mead Johnson.

1. Lish, P. M., and Dungan, K. W.: J. Am. Pharm. A. (Scient. Ed.) 47: 371-375 (May) 1958.
2. Lamphier, T. A.: Am. J. Proctol. 8: 442-444 (Dec.) 1957.

Mead Johnson
Symbol of service in medicine

AC-359M

LONGER M

...IN URINARY TRACT INFECTIONS,

"Thiosulfil" is the one sulfa compound that can be given safely, successfully, and effectively, without interruption over prolonged periods of time[1-5]... especially in recurrent cystitis associated with urinary stasis of pregnancy.

"Thiosulfil"®

BRAND OF SULFAMETHIZOLE

clinical proof and bibliography on following page

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AYERST LABORATORIES

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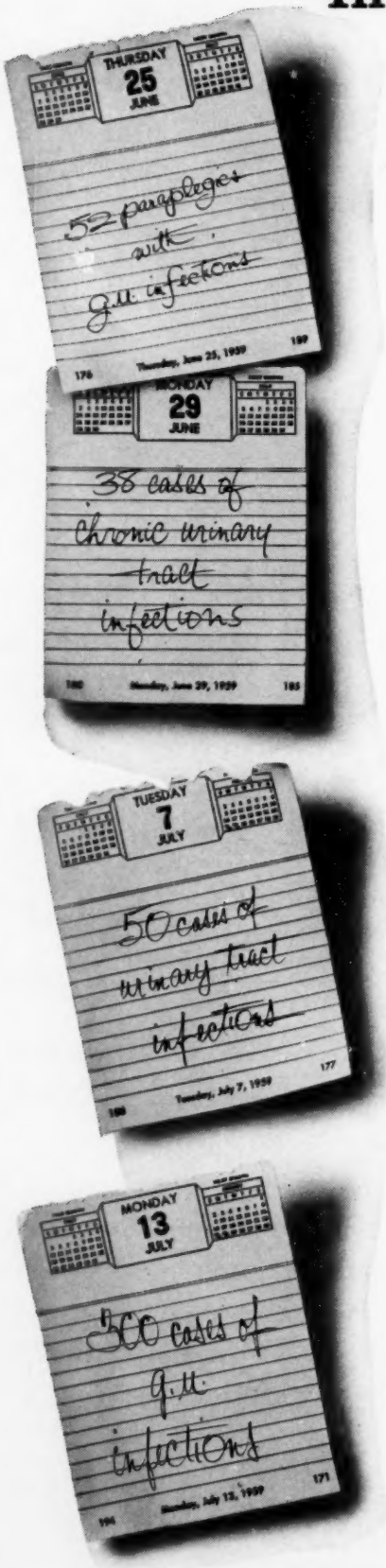
In Urinary Tract Infections



"Thiosulfil"
...for prolonged use

"'Thiosulfil' is a highly soluble sulfonamide derivative which can be administered effectively over a long period of time with minimal toxic manifestation."

1. Cottrell, T.L.C.; Rolnick, D., and Lloyd, F. A.: Rocky Mountain M.J. *56*:66 (Mar.) 1959.

"It ['Thiosulfil'] is useful for palliation in chronic urinary tract infections that are due to pathological conditions which cannot be cured. The drug can be taken over a long period of time with practically no untoward side reactions."

2. Barnes, R. W.: J. Urol. *71*:655 (May) 1954.

"Thiosulfil"
...well tolerated

"'Thiosulfil' was remarkably well tolerated, there being no discontinuation of therapy due to untoward effects, and very few mild reactions were noted.... 'Thiosulfil' is a very valuable adjuvant in the treatment of common urinary infections..."

3. Bourque, J. P. and Joyal, J.: Canad. M.A.J. *68*:337 (Apr.) 1953.

"Thiosulfil"
...safe, effective

"Clinical trial appears to indicate that the drug ['Thiosulfil'] can be tolerated where other sulfa drugs cannot and that it is effective where some others are not....The drug has been given with good results in the presence of urinary retention and severe uremia."

4. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954.

Continued from preceding page

"Thiosulfil"
...potent antibacterial agent

"...'Thiosulfil' is an effective chemotherapeutic agent in urinary tract infections....there was only one failure in the 'Thiosulfil' treated acutely infected group (31 patients)."

5. Hughes, J.; Coppridge, W. M., and Roberts, L. C.: South. M.J. *47*:1082 (Nov.) 1954.

In difficult cases of paraplegics with urinary tract infections, "'Thiosulfil' was ineffective in only 7 per cent [93% effective] of the urinalyses as contrasted to 28 per cent [72% effective] of the urines on [sulfisoxazole] therapy."

1. Cottrell, T. L. C.; Rolnick, D., and Lloyd, F. A.: Rocky Mountain M.J. *56*:66 (Mar.) 1959.

"Thiosulfil" delivers more therapeutic impact at site of infection than any other single or combined sulfa compound. Higher urinary concentrations are achieved. 98% of the drug is present as free, active (nonmetabolized) sulfa[6]...a most efficient sulfa drug with outstanding patient toleration.[4]

6. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, April 6-9, 1959, San Francisco, California.

"Thiosulfil"®

BRAND OF SULFAMETHIZOLE

Usual dosage: Adults, two tablets or two teaspoonfuls q.i.d.

Supplied: Tablets: No. 785 — 0.25 Gm. per tablet (Scored). Bottles of 100 and 1,000.
Suspension: No. 914 — 0.25 Gm. per 5 cc. (teaspoonful). Bottles of 4 and 16 fluidounces.

also available: **"Thiosulfil"®-A**

BRAND OF SULFAMETHIZOLE WITH PHENYLAZO-DIAMINO-PYRIDINE HCl

in urinary tract infection when analgesia is desired

"Thiosulfil"®-A — each tablet contains:
0.25 Gm. sulfamethylthiadiazole and 50 mg. phenylazo-diamino-pyridine HCl.

Usual dosage: Adults, two tablets q.i.d.

Supplied: Tablets: No. 784 — Bottles of 100 and 1,000.

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1959

Pregnancy can be made a happier experience...

Miltown therapy resulted in complete relief from symptoms in 88% of 164 pregnant women complaining of insomnia, anxiety and emotional upsets.[1]

MILTOWN RELIEVES BOTH MENTAL AND MUSCULAR TENSION

- causes no adverse effects on circulatory system, G.I. tract, respiration, or other autonomic function
- does not impair mental faculties, motor control or normal behavior
- *well tolerated throughout pregnancy*[1]

meprobamate (Wallace)

Miltown®

Available in 400 mg. scored and 200 mg. sugar-coated tablets; bottles of 50. Also available as MEPROSPAN® (200 mg. meprobamate *continuous release* capsules).

1. Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec. 9:703, June 1957.

®TRADE-MARK

CM-8647

WALLACE LABORATORIES, *New Brunswick, N. J.*

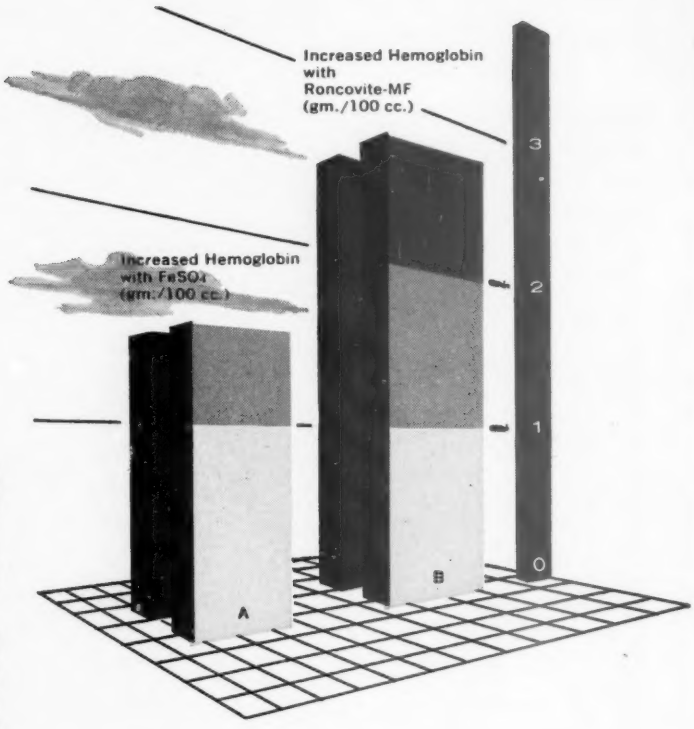
Prompt symptomatic relief
of vaginal itching
in monilial, atrophic, senile, allergic,
and nonspecific trichomonal
vulvovaginitis.[1-5]
CORTRIL®
brand of hydrocortisone
VAGINAL TABLETS
". . . a safe and uniformly
effective method of relieving
genital pruritus in women . . ."[6]
"Relief of pruritus usually
occurred dramatically within
the first 24 hours of treatment."[6]
Supplied: As 10 mg. white tablets
in packages of 10.
Pfizer Science for the world's well-being
PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

References: 1. Blinick, G.: Hydrocortisone vaginal tablets in vaginal pruritus, Obst. & Gynec. *6*:590 (December) 1955. 2. Lang, W. R.: Hydrocortisone vaginal tablets in vaginitis, Postgrad. Med. *21*:320 (March) 1957. 3. Roland, M., Veprovsky, E. C., and Linhart, W.: Hydrocortisone in vaginitis, Obst. & Gynec. *7*:459 (April) 1956. 4. Scheffey, L. C., Rakoff, A. E., and Lang, W. R.: An unusual case of exudative vaginitis treated with local hydrocortisone, Am. J. Obst. & Gynec. *72*:208 (July) 1956. 5. Thomas, H. H.: Inflammatory diseases—vulval and vaginal, Am. Pract. & Digest Treat. *8*:1399 (Sept.) 1957. 6. Finkler, R. S.: Local hydrocortisone therapy of vaginal and vulval pruritus, A. J. Obst. & Gynec. *75*:319 (Feb.) 1958.

LEGEND:

(A) Patients receiving ferrous sulfate 200 mg. q.i.d. showed average increase in hemoglobin of 1.5 gm.

(B) Patients receiving Roncovite-MF (15 mg. cobalt chloride and 100 mg. ferrous sulfate) showed average increase in hemoglobin of 2.7 gm.



Improved iron utilization in anemia

RONCOVITE®-mf

Each tablet contains: Cobalt chloride (Cobalt as Co....3.7 mg.)...15 mg. Ferrous sulfate, exsiccated...100 mg.

Improves iron utilization by enhancing the formation of erythropoietin, the erythropoietic hormone

Recent research[1,2] again emphasizes the role of cobalt as the only clinically proved agent which enhances erythropoietin formation.

The acceleration of erythropoiesis with Roncovite therapy provides optimal utilization of iron.

Acting through this physiologic mechanism, Roncovite (cobalt-iron) therapy results in an increased production of red cells and hemoglobin—a better blood picture—a faster, more complete response than iron alone in the common hypochromic anemias—menstrual anemia—anemia of pregnancy—nutritional anemia of infancy—and in anemia due to chronic infection or inflammation.[3,4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O., and Goldwasser, E.: Ann. Int. Med. *49*:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C., and Bethell, F. H.: J. Lab. & Clin. Med. *52*:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. *1*:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. *113*:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas J. Med. *51*:686 (Oct.) 1955.

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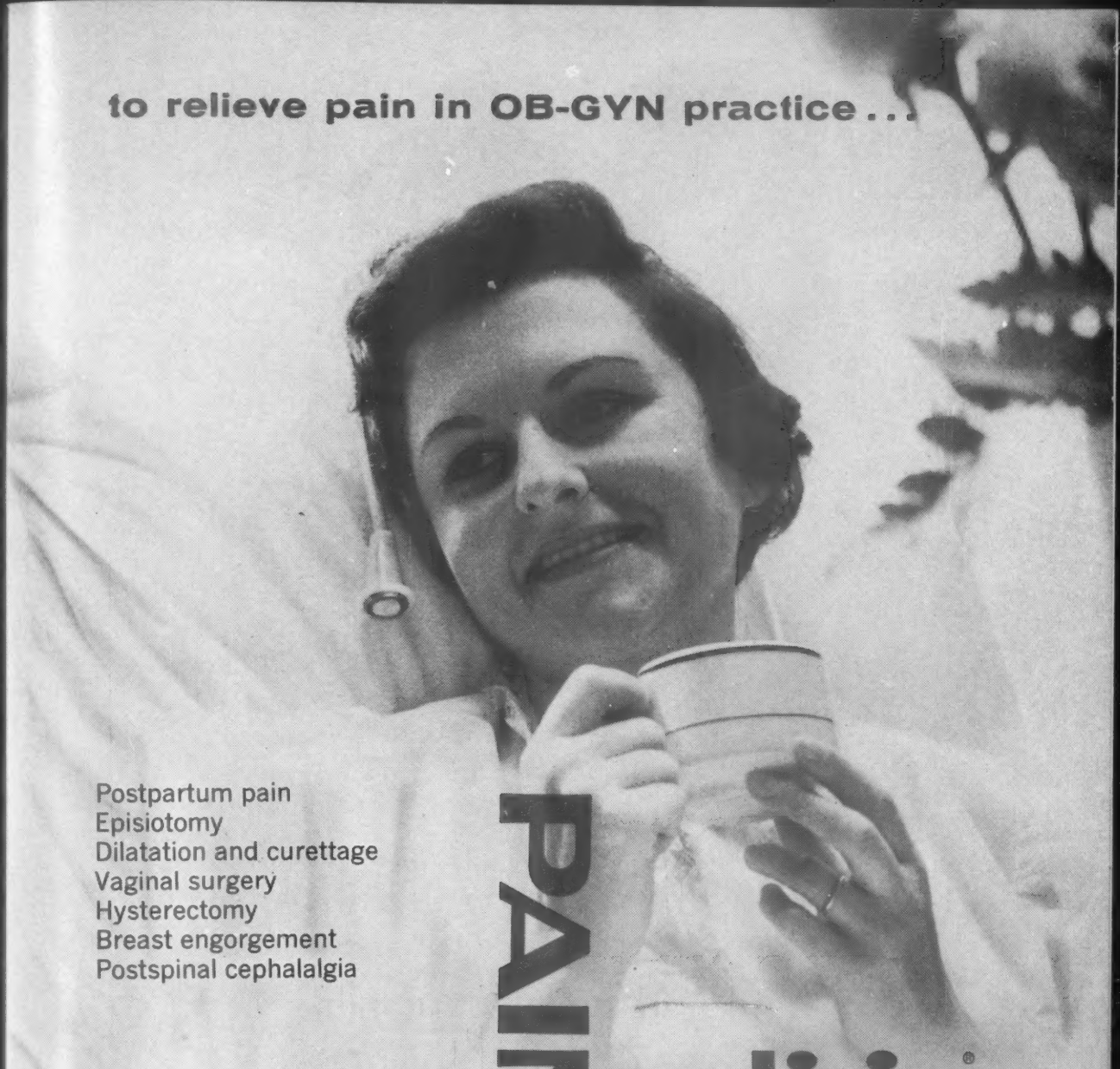
to relieve pain in OB-GYN practice . . .



Postpartum pain
Episiotomy
Dilatation and curettage
Vaginal surgery
Hysterectomy
Breast engorgement
Postspinal cephalalgia

remember PAIN Zactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

After using ZACTIRIN in 92 obstetrical and postsurgical gynecological patients, Roden and Haugen[1] conclude from the patients' own reports: *In obstetrical patients*—"an effective analgesic for the usual types of pain occurring during the postpartum period." *In gynecological patients*—"satisfactorily relieves mild or moderate post-operative pain occurring as the result of major and minor surgical procedures." *Side-effects*—"infrequent and mild and did not necessitate discontinuing use."

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

1. Roden, J.S., and Haugen, H.M.: Missouri Med. *55*:128 (Feb.) 1958.

- *original Wyeth non-narcotic analgesic plus anti-inflammatory action*
- *orally administered*
- *prompt, long action—relief equivalent to that of codeine*

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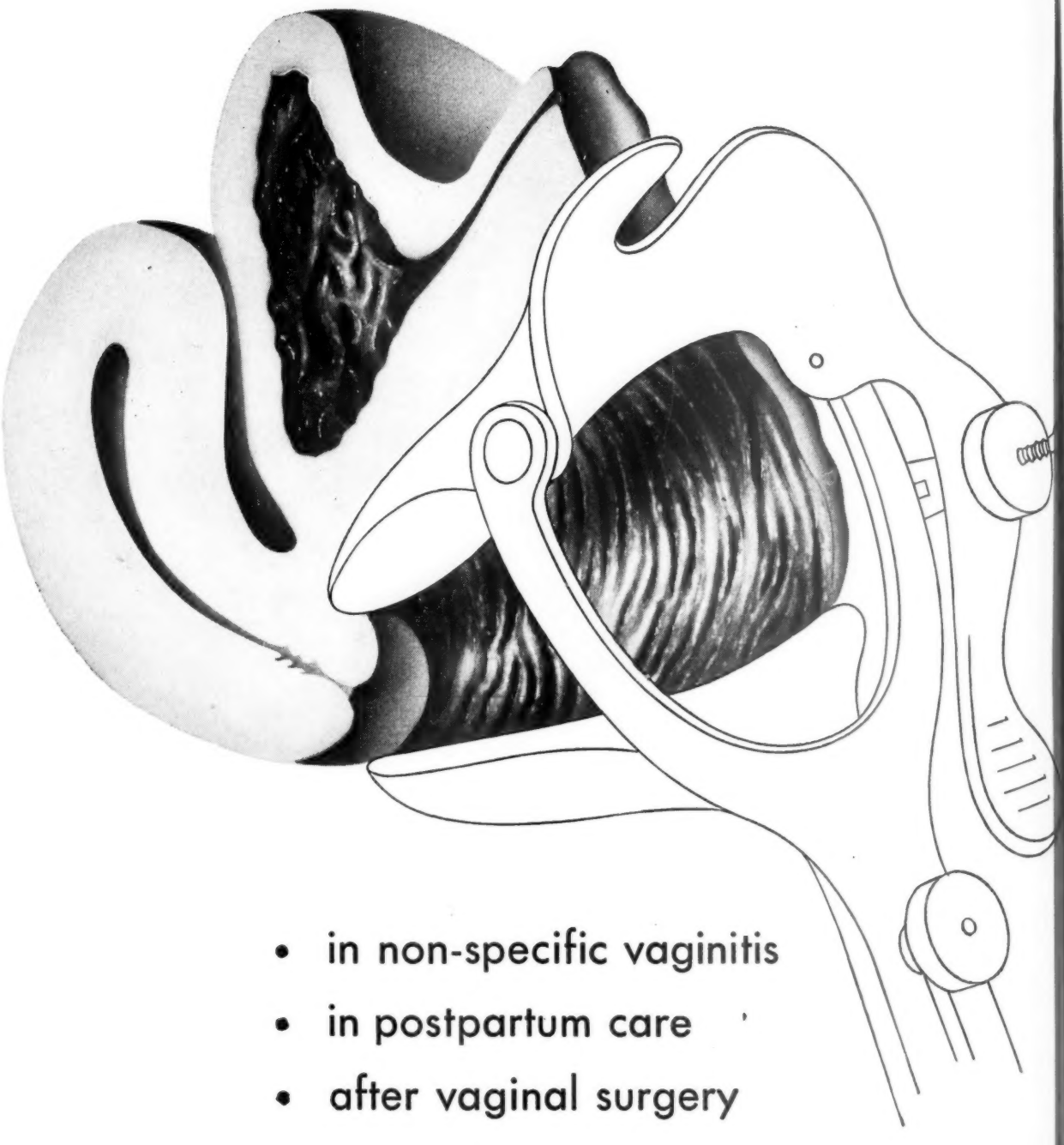

- in non-specific vaginitis
- in postpartum care
- after vaginal surgery

Triple Sulfa Cream

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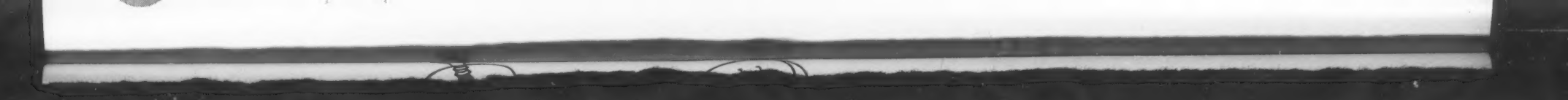

CHELATED IRON FOR MORE EFFICIENT ORAL THERAPY

■ outstandingly free from g.i. irritation ■ does not stain teeth [when given as a liquid] ■ can be taken **any** time – between meals without irritation, or at mealtime without impaired utilization ■ compatible with ulcer medication, and does not cause added irritation ■ safest iron to have in the home because of chelate-controlled absorption ■ and – clinically confirmed as an effective hematinic [Franklin et al.: J.A.M.A. 166:1685, 1958]

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Brand of Iron Choline Citrate* Trademark

CHELATED
the new way
to give oral iron

Tablets — 1 tablet t.i.d. furnishes 120 mg. iron

Pediatric Drops — 1 cc. furnishes 16 mg. iron

also: **CHĒL-IRON PLUS Tablets** — chelated iron **plus** B_{12}, folic acid, other B vitamins, and C.

REFER TO PDR
PAGE 681

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"Chelate" describes a chemical structure in which metallic ions are "encircled" and their physicochemical properties thereby altered. **Chelated iron** (as iron choline citrate*) is unusually soluble; nonionizable; not precipitated by variations in g.i. tract pH, protein, phosphate, or alkali; yet is readily available for hemopoiesis on physiologic demand.

*U. S. PAT. 2,575,611

in vaginitis

IMPROVED

TRICOFURON®

destroys all 3 *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

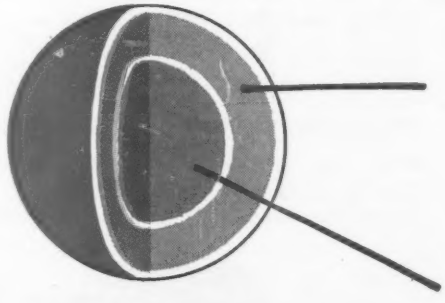
℞ NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

the complaint: "nervous indigestion"

the diagnosis: any one of several nonspecific gastrointestinal disorders requiring relief of symptoms by sedative-antispasmodic action with concomitant digestive enzyme therapy. **the prescription:** a new formulation, incorporating in a single tablet the actions of Donnatal and Entozyme. **the dosage:** two tablets three times a day, or as indicated.



the formula: *in the gastric-soluble outer layer:*

Hyoscyamine sulfate	0.0518 mg.
Atropine sulfate	0.0097 mg.
Hyoscine hydrobromide	0.0033 mg.
Phenobarbital (1/8 gr.)	8.1 mg.
Pepsin, N.F.	150 mg.

in the enteric-coated core:

Pancreatin, N.F.	300 mg.
Bile salts	150 mg.

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eliminate the cause of iron intolerance

NEW LOWEST DOSE IRON...

SIMRON

...only 30 mg. of iron daily provides full therapeutic response

IRON OVERLOAD IS UNNECESSARY—this unusually low-dose iron (30 mg. instead of the usual 100 mg. plus) provides the hemoglobin rise necessary to correct iron deficiency anemia. The reason is a dramatic new aid to iron absorption.*

AVOID GASTRIC IRRITATION—nausea/diarrhea... even the black stool which can hide a serious condition... are usually absent.

PRESCRIBE SIMRON BETWEEN MEALS—the daily dose is one capsule (containing 10 mg. iron as ferrous gluconate) t.i.d.

TRADEMARKS: 'SACAGEN,' 'SIMRON' *Sacagen—400 mg. per capsule.

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THE WM. S. MERRELL COMPANY

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all through pregnancy . . .
a cheerful outlook
without autonomic toxicity reactions

relieves
anxiety
insomnia
fretfulness
tension headache
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One of your safest adjuncts for
successful management of pregnancy

Equanil®
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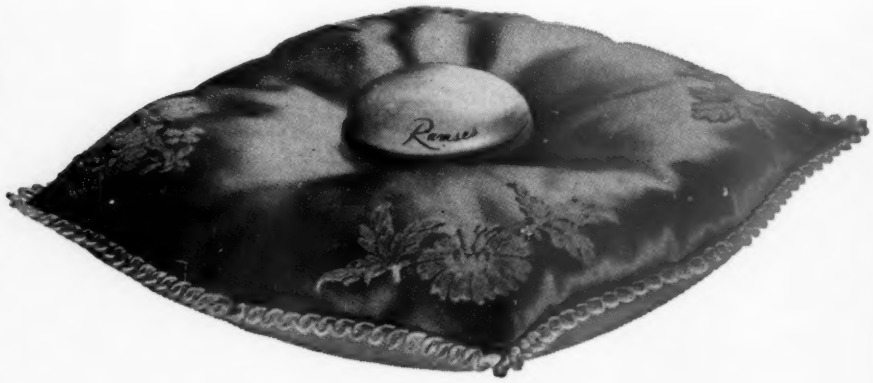

You are giving very special physical comfort to your patients with RAMSES® Diaphragm and Jelly* because the RAMSES Diaphragm has a soft, cushioned rim and is flexible in all planes to permit complete freedom of motion, and because RAMSES Jelly is uniquely suited for use with the RAMSES Diaphragm. It is not a static jelly or cream, but flows freely over the rim and surface to lubricate the diaphragm, add comfort, and protect the patient for *ten full hours.*

With **RAMSES *Diaphragm and Jelly*** you are also providing essential inner security, since your patient is assured she can plan her family according to her wishes, safe in the knowledge that she is using not only the most reliable method — diaphragm and jelly — but the most comfortable and reliable diaphragm and jelly, RAMSES. As Tietze[1] has pointed out, the diaphragm and jelly method reduces the likelihood of conception by at least 98 per cent.

After fitting the diaphragm, prescribe the complete unit — the new RAMSES "TUK-A-WAY"® Kit #701 with diaphragm, introducer and jelly in an attractive new zipper case which opens top and side.

Ramses®

For those who put a special value on simplicity and convenience, such as "just marrieds," new IMMOLIN® Cream-Jel for use *without a diaphragm* is now available. IMMOLIN forms an impenetrable matrix in which sperm are trapped, lose vitality and die. The first published study[2] on IMMOLIN covering 1,729 patient-exposure months shows a low rate of 2.01 unplanned pregnancies per 100 woman-years of exposure.

JULIUS SCHMID, INC., 423 West 55th Street, New York 19, N. Y.

1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.
2. Goldstein, L. Z.: Obst. & Gynec. 10:133 (Aug.) 1957.

*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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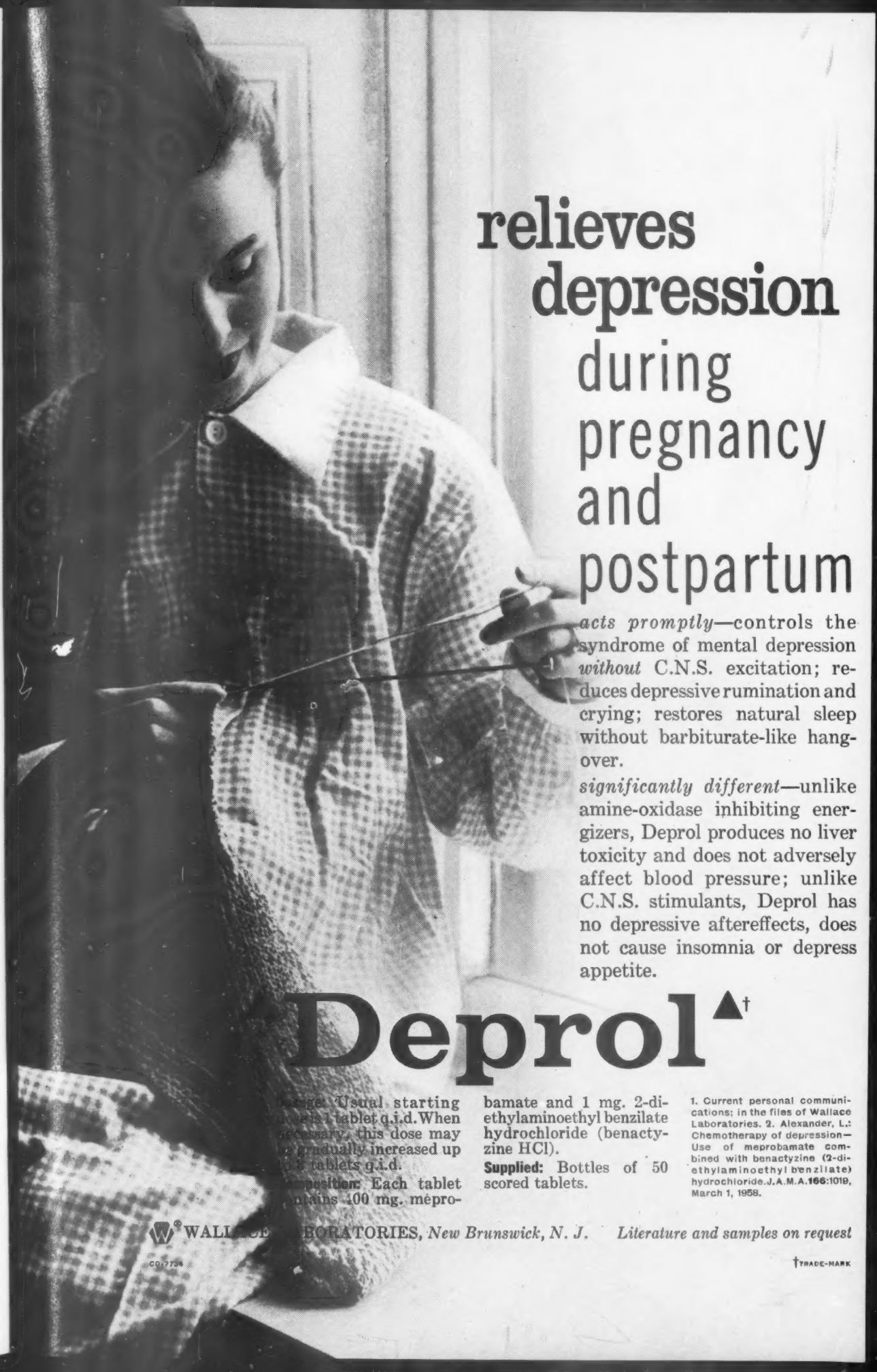

relieves depression during pregnancy and postpartum

acts promptly—controls the syndrome of mental depression *without* C.N.S. excitation; reduces depressive rumination and crying; restores natural sleep without barbiturate-like hangover.

significantly different—unlike amine-oxidase inhibiting energizers, Deprol produces no liver toxicity and does not adversely affect blood pressure; unlike C.N.S. stimulants, Deprol has no depressive aftereffects, does not cause insomnia or depress appetite.

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...ge: Usual starting ...ial tablet q.i.d. When ...essary, this dose may ... gradually increased up ... tablets q.i.d.

...position: Each tablet ...tains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Current personal communications; in the files of Wallace Laboratories. 2. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958.

WALL... LABORATORIES, *New Brunswick, N. J.* *Literature and samples on request*

CO-1774

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Classic Treatment in Hypertension*

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid®* + *Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.
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alseroxylon 1 mg. and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

* ***Because***

RAUWILOID provides effective Rauwolfia action virtually free from serious side effects ... the smooth therapeutic efficacy of Rauwiloid is associated with a lower incidence of certain unwanted side effects than is reserpine...and with a lower incidence of depression. Tolerance does not develop.

RAUWILOID can be initial therapy for most hypertensive patients...Dosage adjustment is rarely a problem.

Riker
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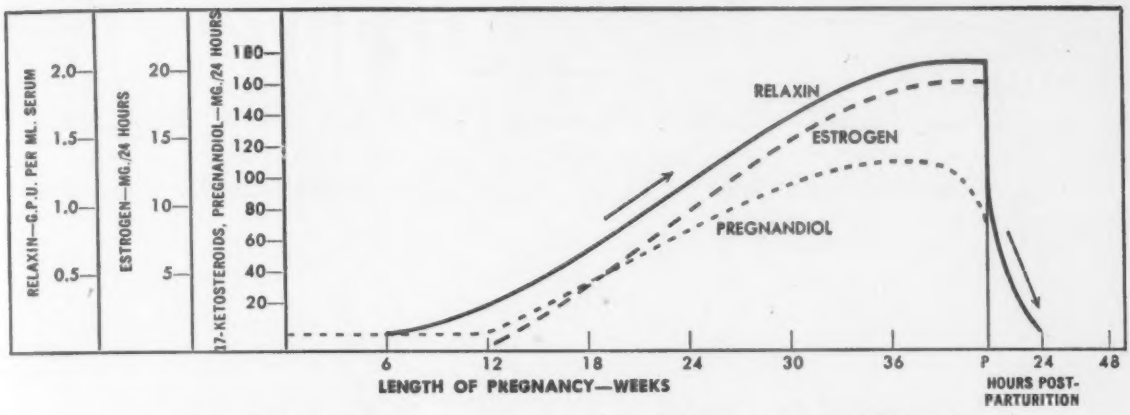

to reinforce the normal physiology of childbirth

Cervilaxin

(relaxin, National)

for shorter labor, easier delivery

Clinical studies of relaxin as a cervical relaxant in 564 parturient women—

Israel[1]	20 patients	"preliminary clinical impression is highly favorable"
Eichner[2]	32 patients	"definite softening . . ."
Hodgkinson[3]	20 patients	"impressed with the soft state of the cervix."
Eisenberg[4]	117 patients	"rapid softening and dilatability"
Pou de Santiago[5]	20 patients	"dilatation not only at the cervix but also in the perineum"
Birnberg[6]	258 patients	"Cervilaxin alone produces a marked softening of the cervix"
Stone[7]	97 patients	"relaxin does soften the cervix"
Total:	564 patients	

In spontaneous or induced labor at term, *Cervilaxin*—the third ovarian hormone—aids the normal physiology of parturition, softening and relaxing the cervix, safely, without side effects, to help

1. **shorten labor**
2. **reduce fetal damage and maternal complications**
3. **make the use of oxytocin safer**

Cervilaxin should be administered by intravenous drip, and is supplied in 2-ml. vials containing 20 mg./ml., with detailed instructions in each package.

References: 1. Israel, S.L.: Personal Communication. 2. Eichner, E., *et al.*: Am. J. Obst. & Gynec. *71*:1035, 1956. 3. Hodgkinson, C.P.: Am. J. Obst. & Gynec. *71*:1035, 1956. 4. Eisenberg, L.: J.A.O.A. *57*:146, 1957. 5. Pou de Santiago, A.: Peruvian Obst. & Gynec. Soc., 2nd Uruguayan Conference on Obst. & Gynec., 1957. 6. Birnberg, C.H., and Abitbol, M.M.: Obst. & Gynec. *10*:366, 1957. 7. Stone, M.L.: Effects of Relaxin on Term and Premature Labor, Conf. on The Uterus, The New York Academy of Sciences, Feb. 12-15, 1958.

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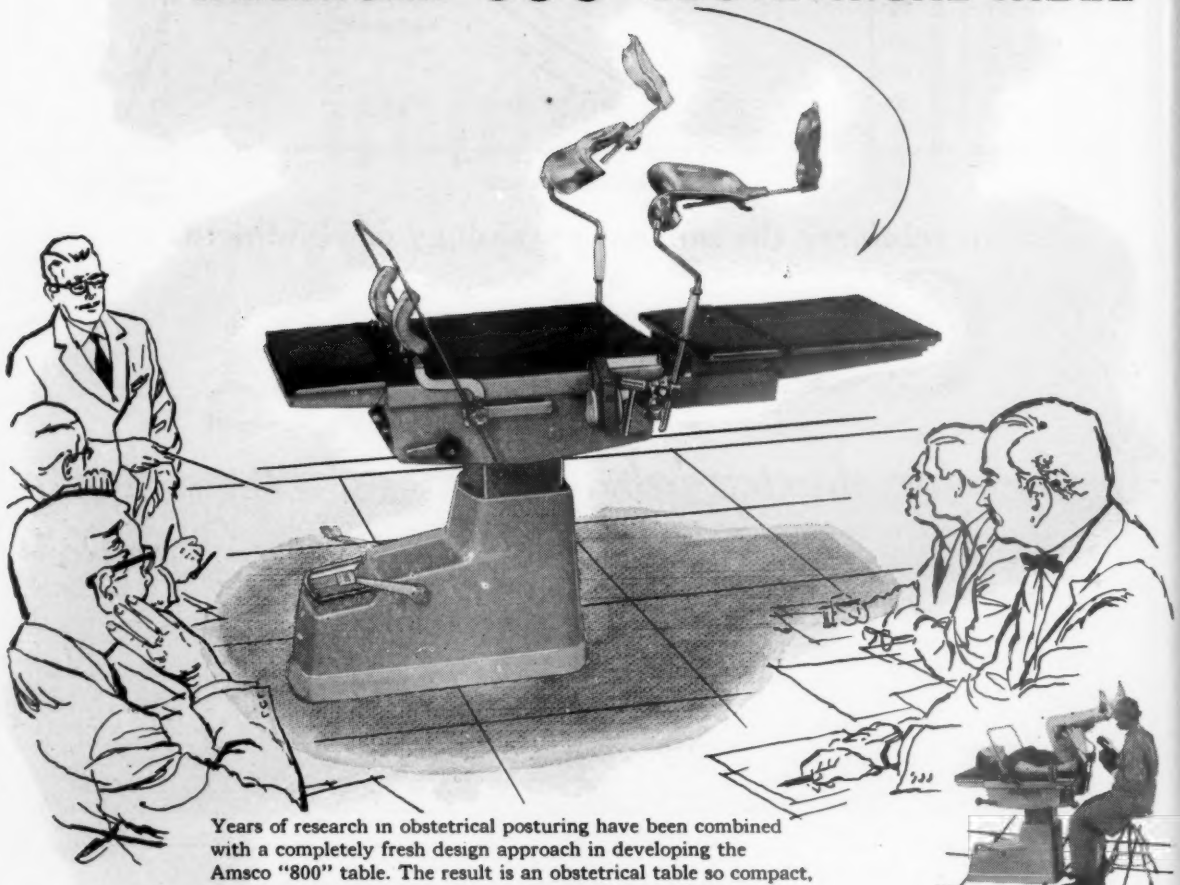
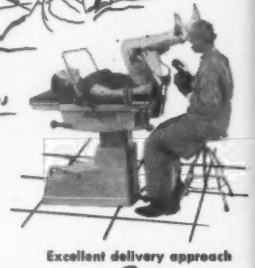
AMERICAN "800" OBSTETRICAL TABLE



Years of research in obstetrical posturing have been combined with a completely fresh design approach in developing the Amsco "800" table. The result is an obstetrical table so compact, so maneuverable and so efficient as to be truly revolutionary in its advantages for operative as well as perineal route delivery.

From the narrow, flowing lines of the flexible top to the *permanent* or *portable* power base . . . the "800" is *new*.



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Every Feature —

- **finger-tip controls**
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- **retractable 12" delivery shelf**
- **ratchet type legholder sockets**
- **flexible head and foot sections**
- **wide perineal opening for postpartum drainage**

. . each is new, exclusive and vital to the convenience of the obstetrician and the welfare of the patient.

Maneuverable table top

Every hospital and every obstetrician will have a direct interest in this dramatically better table. Fully illustrated brochure TC-224-R is available without obligation.

Unobstructed surgical approach

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"...SPINAL ANESTHESIA...used wisely and properly... should produce less complications than any other form of anesthesia."[1]

for dependable spinal anesthesia

PONTOCAINE®

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"... the most universally satisfactory and adaptable for the production of spinal anesthesia of a wide variety of types. Whether the 1 per cent, 20 mg. ampul solution or the Niphanoid preparation is used is a matter of preference."[1]

Spinal anesthesia with Pontocaine is safer[1-5] and much more economical[6] than with most forms of general anesthesia.

Pontocaine is available as:

- 10, 15 and 20 mg. Niphanoid® ampuls
- 1% solution, ampuls of 2 cc. (20 mg.)
- 0.3% hyperbaric solution in dextrose, ampuls of 5 cc. (15 mg.)
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- 0.15% solution for caudal and infiltration analgesia, vials of 100 cc.

Also available: 250 mg. Niphanoid ampuls for preparing solutions for caudal, infiltration or nerve block analgesia.

1. Dillon, J. B.: Spinal Anesthesia, Springfield, Charles C Thomas, 1958, pp. 3, 22.
2. Whitacre, R. J., in Hale, D. E.: Anesthesiology, Philadelphia, F. A. Davis Co., 1954, p. 432.
3. Vandam, L. D. and Dripps, R. D.: *J.A.M.A.* 161:586, June 16, 1956.
4. Ochsner, A. J.: *South. M. J.* 50:1156, Sept., 1957.
5. Ausherman, H. M.: *M. Times* 85:1363, Dec., 1957.
6. Hingson, R. A., Ross, E. F., Castley, E. C.: *Western J. Surg.* 65:375, Nov.-Dec., 1957.

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NOW

...a new way to relieve pain and stiffness in muscles and joints

INDICATED IN:

- MUSCLE STIFFNESS
- LUMBOSACRAL STRAIN
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- LOW BACK PAIN
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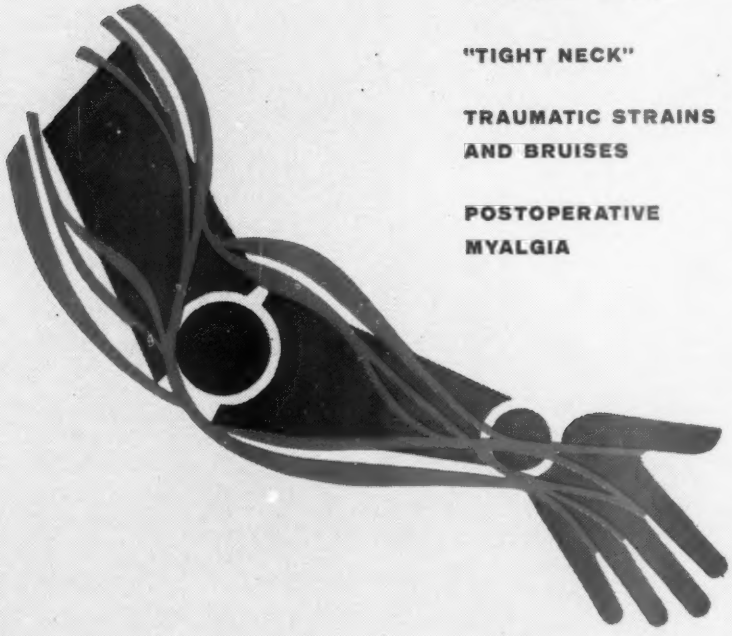
- "TIGHT NECK"
- TRAUMATIC STRAINS AND BRUISES
- POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids ■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

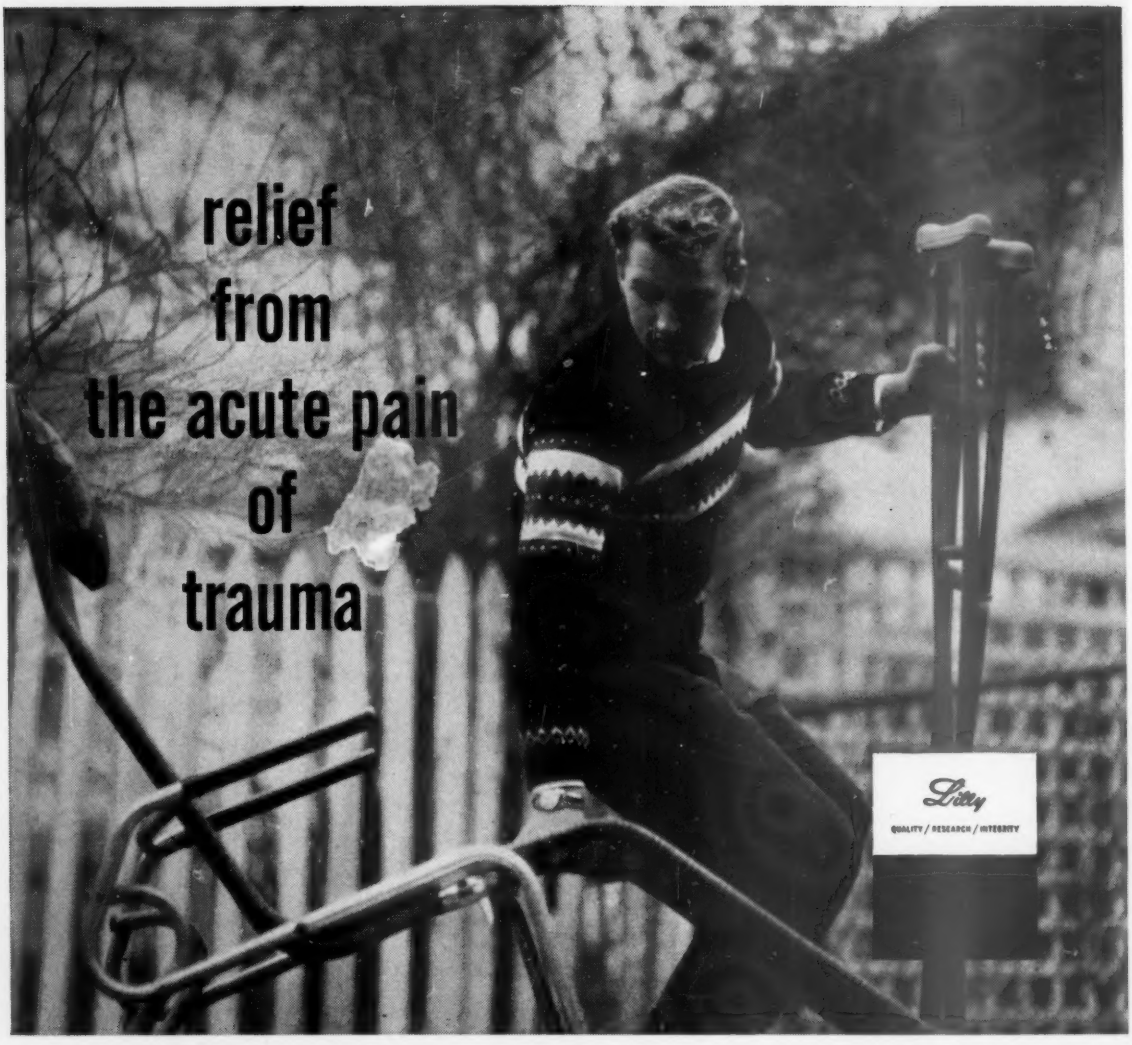
ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.



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Darvon Compound combines in a single Pulvule® the analgesic action of Darvon with the antipyretic and anti-inflammatory benefits of A.S.A.® Compound (acetylsalicylic acid and acetophenetidin compound, Lilly). When inflammation is present, Darvon Compound reduces discomfort to a greater extent than does either analgesic given alone.

Usual dosage: 1 or 2 Pulvules three or four times daily.

Also available: Darvon, in 32 and 65-mg. Pulvules.

Usual dosage: 32 mg. (approximately 1/2 grain) every four hours or 65 mg. (1 grain) every six hours.

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Mornidine is supplied as tablets of 5 mg. and as ampuls of 5 mg. (1 cc.).

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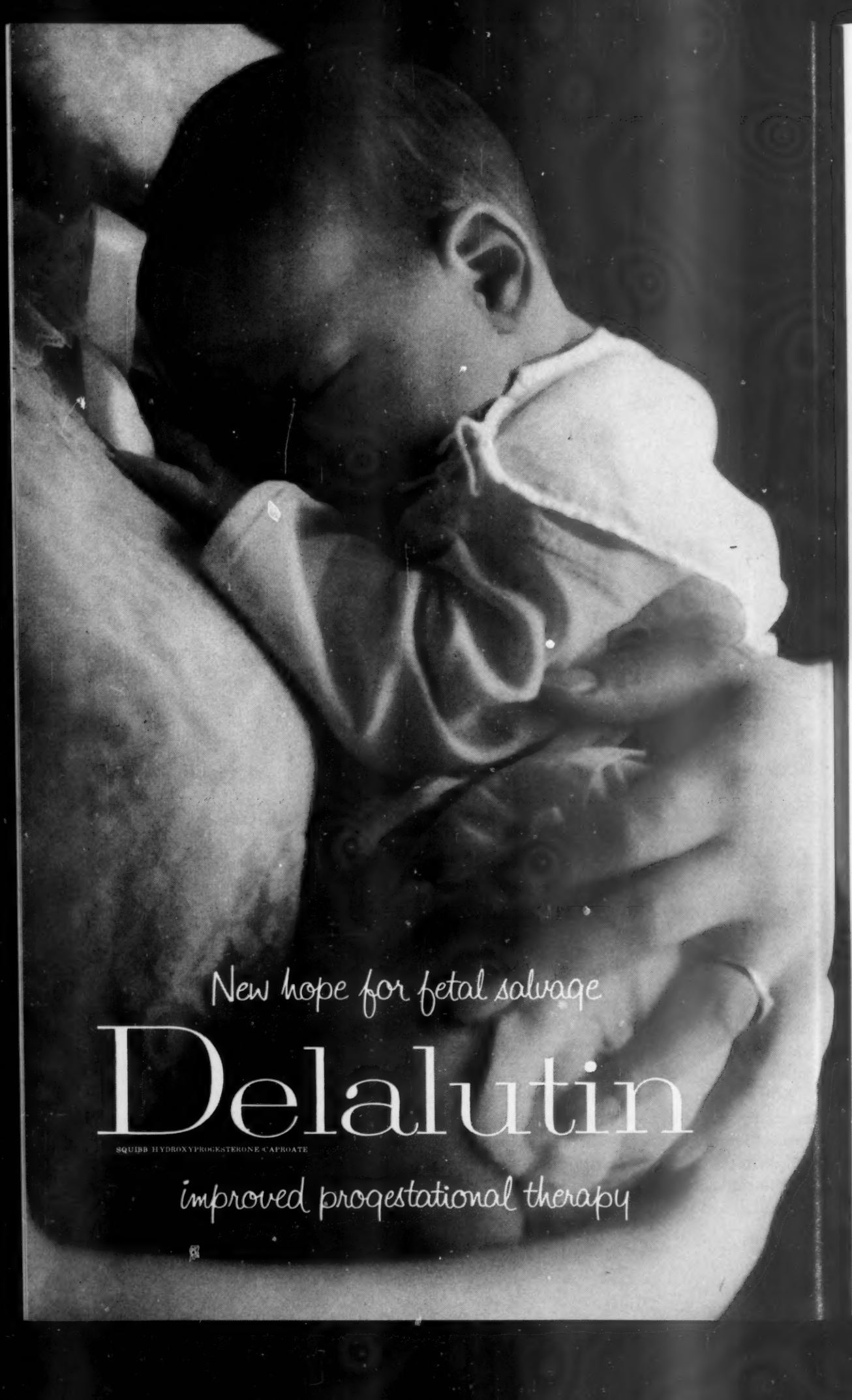
New hope for fetal salvage
Delalutin
SQUIBB HYDROXYPROGESTERONE CAPROATE
improved progestational therapy

The results of administering Delalutin before the 12th week of gestation to 82 women with habitual abortion were reported recently by Reifenstein.[1] Every patient had experienced at least three consecutive abortions immediately preceding the treated pregnancy. More than 68% of these women were delivered successfully and uneventfully following Delalutin therapy.

Boschann,[2] in a study of pregnancies with threatened abortion, found that:

37% of 73 pregnancies were carried to term without progestational therapy
64% of 42 pregnancies were salvaged by progesterone
83% of 73 pregnancies were salvaged by Delalutin

Eichner,[3] found that with Delalutin fetal salvage of infants below term weight (1000 to 2000 gm.) was significantly improved.
108 (76%) of 142 babies of this birth weight survived without progestational therapy.
16 (100%) of 16 babies of this birth weight survived with Delalutin therapy.
A comparison study was made of a group of repeated aborters treated with Delalutin, and a group with a similar history treated with bed rest and sedation.[4] Pregnancy salvage with Delalutin was twice that of the control group. Delalutin was found to be "highly active," well-tolerated and long-acting.

Delalutin offers these advantages over other progestational agents:

- longer-acting and more sustained therapy
- more effective in producing and maintaining a completely matured secretory endometrium
- no androgenic effect
- more concentrated solution requires injection of less vehicle
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- requires fewer injections
- low viscosity makes administration easier

DELALUTIN is also potent and safe therapy for: threatened abortion; postpartum after-pains; amenorrhea, primary and secondary; dysfunctional uterine bleeding not associated with genital malignancy; infertility with inadequate corpus luteum function; production of secretory endometrium and desquamation during estrogen therapy; premenstrual tension; dysmenorrhea; cyclomastopathy, mastodynia, adenosis and chronic cystic mastitis.

Administration and Dosage: **Because of its low viscosity, Delalutin may be administered with a small gauge needle (deep intragluteal injection). Complete information on administration and dosage is supplied in the package insert.**

Supply: **Delalutin is available in vials of 2 and 10 cc., each cc. containing 125 mg. of hydroxyprogesterone caproate in sesame oil, and benzyl benzoate.**

References: 1. Reifenstein, E. C., Jr.: *Annals N. Y. Acad. Sci.* 71:762 (July 30) 1958. 2. Boschann, H-W.: *ibid.*, p. 727. 3. Eichner, E.: *ibid.*, p. 787. 4. Hodgkinson, C. P.; Igna, E. J., and Bukeavich, A. P.: *Am. J. Obst. and Gyn.* 76:279, 1958.

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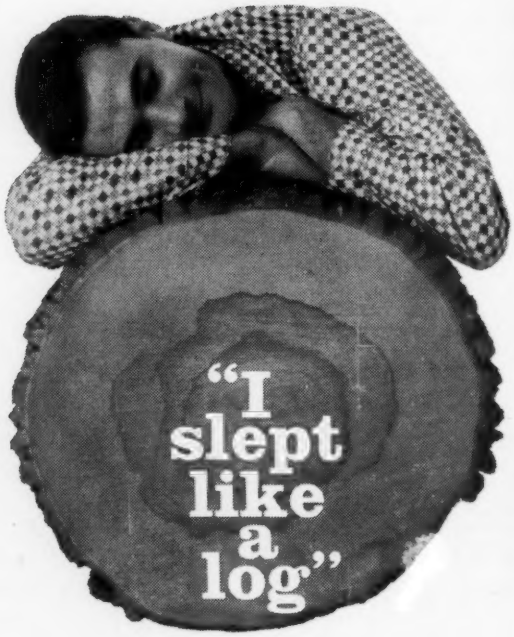

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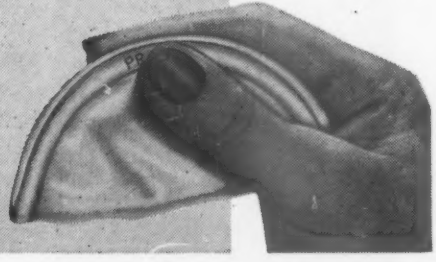

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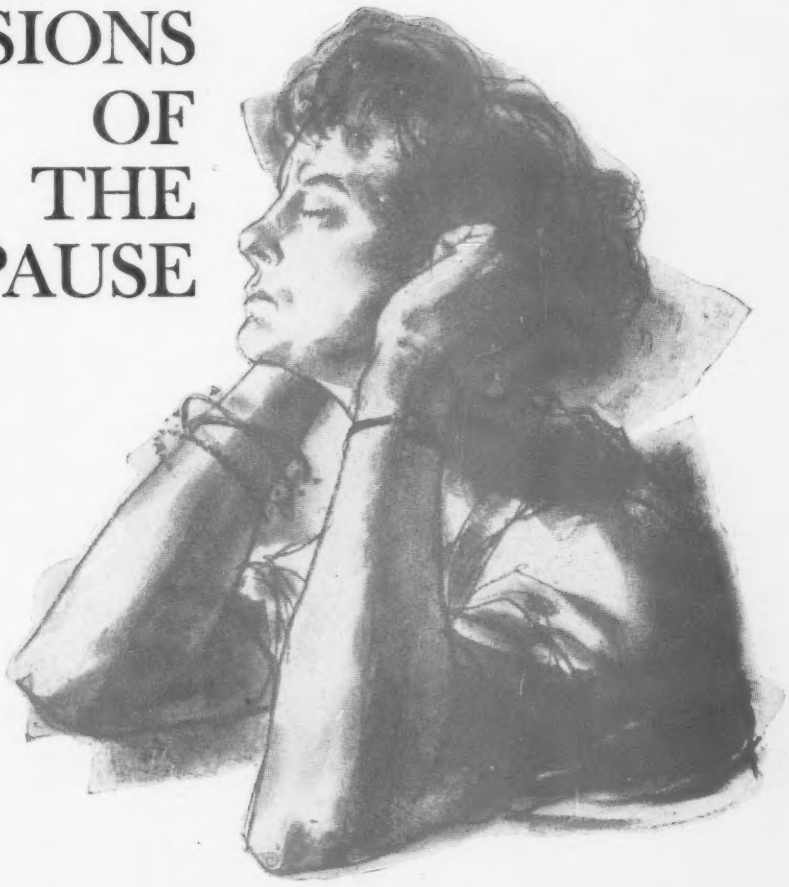

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1. Farquharson, R. F.: The menopausal patient. M. Rec. & Ann. 49:196, Feb. 1955.

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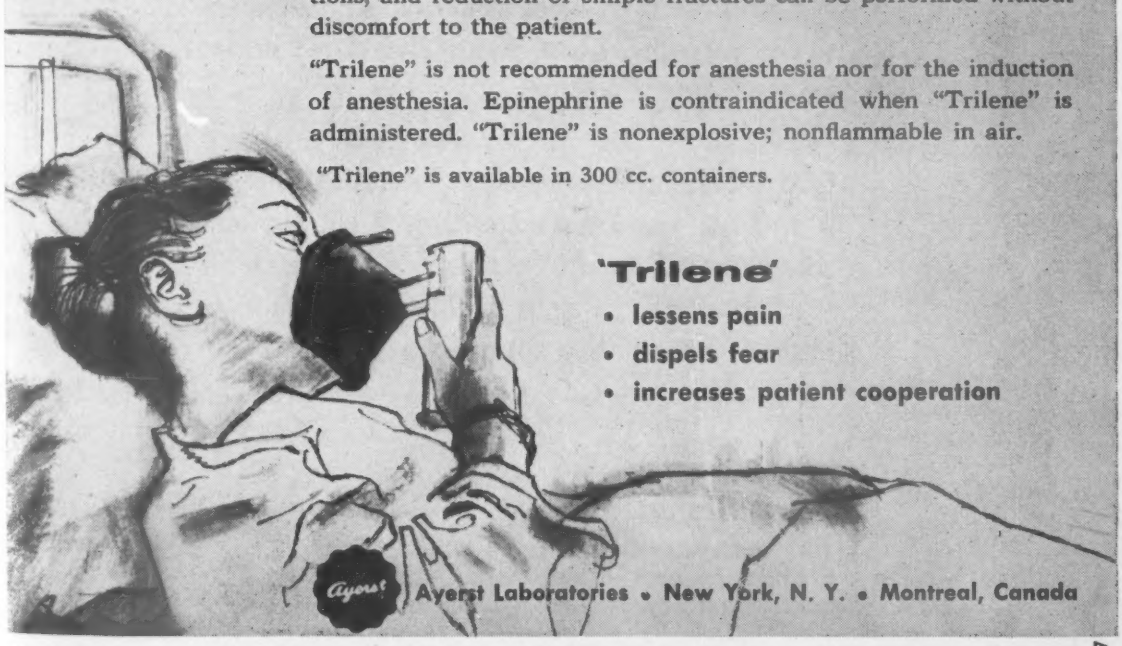

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>
> "In the United States an average diet containing approximately 40 per cent of the calories in the form of fat has been consistent with the attainment of one of the best health patterns in the world."

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*The Role of Dietary Fat in Human Health: A Report of the Food and Nutrition Board, National Academy of Sciences—National Research Council, Washington, D. C., Publication 575, 1958.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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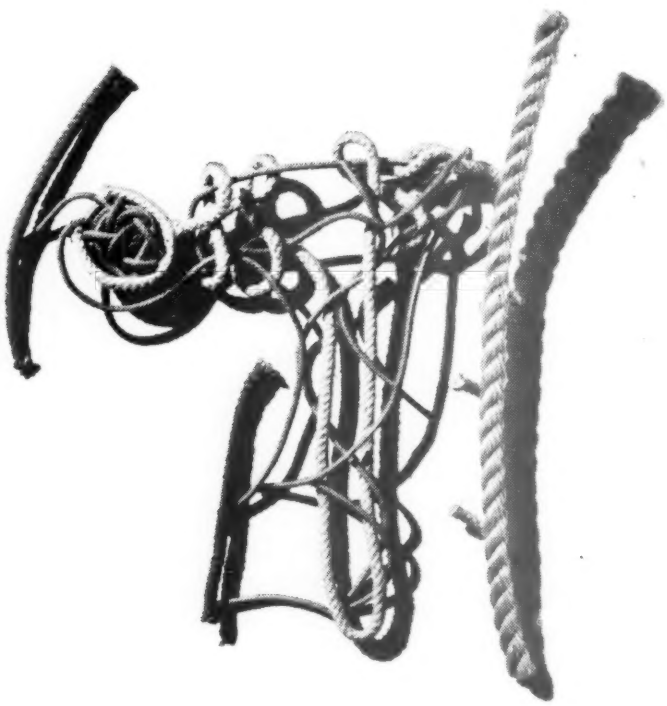

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pyelonephritis

"the most important concept is that it is a tubular disease"[1]

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References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Jawetz, E., et al.: A.M.A. Arch. Int. M. 100:549, 1957.

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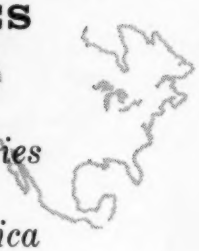

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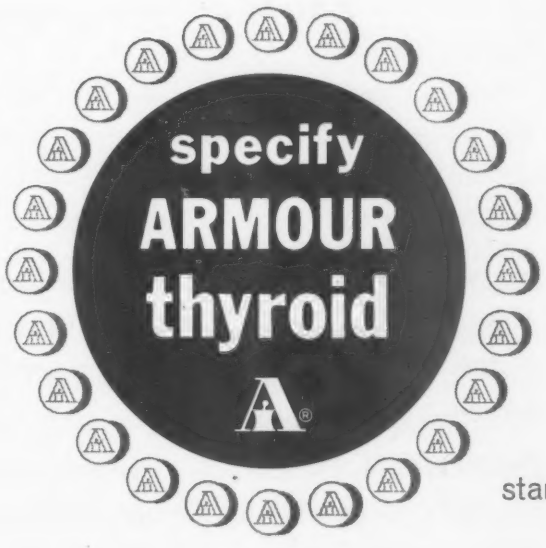

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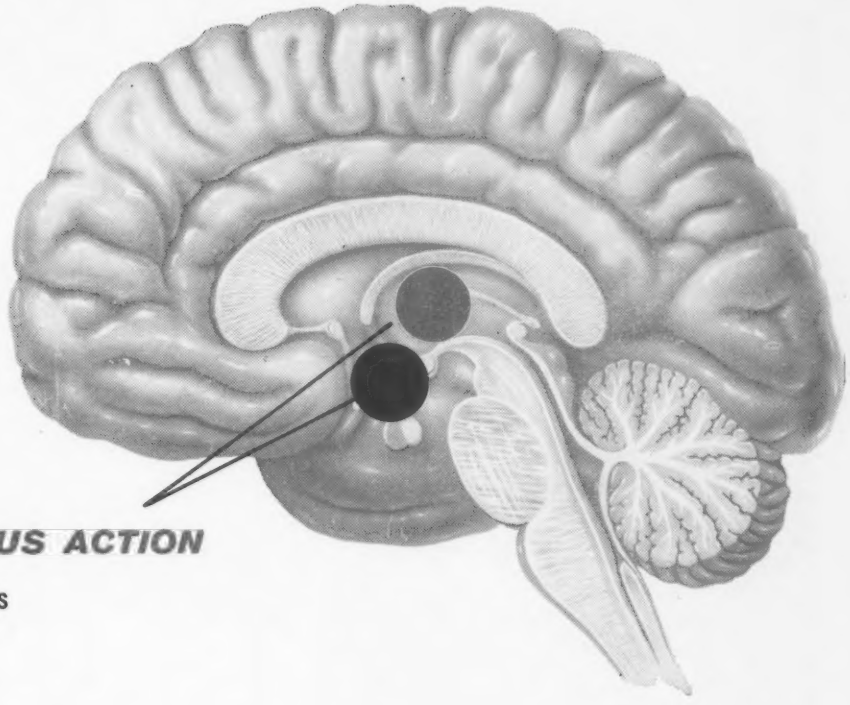

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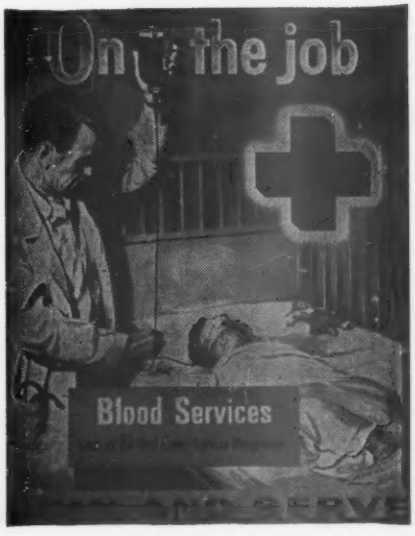

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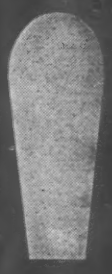

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